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The Western Journal of Medicine

VOLUME 153 • NUMBER 1 JULY 1990

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Investigators' evaluations confirm hair growth in male pattern baldness of the vertex

ROGAINE® Topical Solution (minoxidil 2%) is the *first* prescription medication proved effective for male pattern baldness of the vertex. The effect on frontal baldness has not been adequately studied.

Evidence of growth was demonstrated by physician evaluations of 1,431 patients in 27 centers across the United States. Patients were placed on ROGAINE or placebo and evaluated each month for four months. Response was judged to be no growth, new vellus (baby) hair, or minimal, moderate, or dense growth.

In addition, after the placebo group was discontinued, continuous application of ROGAINE over an additional eight months was evaluated to determine if nonvellus growth could be sustained.

START OF STUDY

START OF STUDY

START OF STUDY

Examples of minimal, moderate, and dense growth as evaluated by investigators

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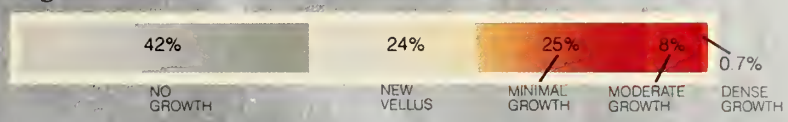
MODERATE GROWTH

DENSE GROWTH

Four-Month Phase

At the end of four months, 34% of 714 patients treated with ROGAINE were evaluated as showing minimal, moderate, or dense growth, while 20% of 717 patients showed minimal, moderate, or dense growth with placebo, a highly significant difference ($P<.0005$).

Rogaine (714)



Placebo (717)

Non-Placebo-Controlled Continuation Phase

After 12 months, dense growth was observed in 8% of the 619 patients treated with ROGAINE, moderate growth in 31%, and minimal growth in 37%. Approximately one fourth of patients showed only vellus hair growth or no growth.

Rogaine (619)

Compliance is Essential

The multicenter studies indicate that a period of *four months or longer* of daily b.i.d. applications of ROGAINE is usually necessary before evidence of hair growth is apparent. Hair growth continued to increase in study subjects over months 5 through 12.

Continuous use is necessary to maintain hair growth. Newly grown hair returns to the untreated state three to four months after cessation of therapy with ROGAINE.

Please see last page for brief summary of prescribing information.

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INDICATIONS AND USAGE
Male pattern baldness (alopecia androgenetica) of the vertex of the scalp No effect has been seen on frontal baldness At least four months of treatment are generally required before evidence of hair growth can be expected, further growth continues through one year. The new growth is not permanent, cessation of treatment will lead to its loss in a few months

CONTRAINDICATIONS
Hypersensitivity to minoxidil, propylene glycol or ethanol

WARNINGS
1 *Need for normal scalp* Before starting treatment, make sure that the patient has a normal, healthy scalp Local abrasion or dermatitis may increase absorption and hence the risk of side effects
2 *Potential adverse effects* Although extensive use of topical minoxidil has not revealed evidence that enough minoxidil is absorbed to have systemic effects, greater absorption due to misuse, individual variability or unusual sensitivity could, at least theoretically, produce a systemic effect
Experience with oral minoxidil has shown the following major cardiovascular effects (Review the package insert for LONITEN® Tablets for details):
—salt and water retention, generalized and local edema
—pericardial effusion, pericarditis, tamponade
—tachycardia
—increased incidence of angina or new onset of angina
Patients with underlying heart disease, including coronary artery disease and congestive heart failure, would be at particular risk of these potential effects Additive effects could also emerge in patients being treated for hypertension
Potential patients should have a history and physical, should be advised of potential risks and a risk/benefit decision should be made Heart patients should realize that adverse effects may be especially serious Alert patients to the possibility of tachycardia and fluid retention, and monitor for increased heart rate, weight gain or other systemic effects

PRECAUTIONS
General Precautions Monitor patients one month after starting ROGAINE and at least every six months afterward Discontinue ROGAINE if systemic effects occur The alcohol base will burn and irritate the eye If ROGAINE reaches sensitive surfaces (eg, eye, abraded skin and mucous membranes) bathe with copious cool water.
Avoid inhaling the spray
Do not use in conjunction with other topical agents such as corticosteroids, retinoids and petrolatum or agents that enhance percutaneous absorption ROGAINE is for topical use only Each mL contains 20 mg minoxidil and accidental ingestion could cause adverse systemic effects
Decreased integrity of the epidermal barrier caused by inflammation or disease of the skin, eg, excoriations, psoriasis or severe sunburn, may increase minoxidil absorption
Patient Information. A patient information leaflet is included with each package and in the full product information
Drug Interactions. No drug interactions are known Theoretically, absorbed minoxidil may potentiate orthostatic hypotension in patients taking guanethidine.
Carcinogenesis, Mutagenesis and Impairment of Fertility No carcinogenicity was found with topical application Oral administration may be associated with an increased incidence of malignant lymphomas in female mice and hepatic nodules in male mice In rats, there was a dose-dependent reduction in conception rate
Pregnancy Category C: ROGAINE should not be used by pregnant women.
Labor and Delivery The effects are not known.
Nursing Mothers. ROGAINE should not be administered
Pediatric Use Safety and effectiveness have not been established under age 18

ADVERSE REACTIONS
ROGAINE was used by 3510 patients in placebo-controlled trials Except for dermatologic events, no individual reaction or reactions grouped by body systems appeared to be increased in the minoxidil-treated patients
Respiratory (bronchitis, upper respiratory infection, sinusitis) 5 95%, **Dermatologic** (irritant or allergic contact dermatitis) 5 27%, **Gastrointestinal** (diarrhea, nausea, vomiting) 3 42%, **Neurology** (headache, dizziness, faintness, light-headedness) 2 56%, **Musculoskeletal** (fractures, back pain, tendinitis) 2 17%, **Cardiovascular** (edema, chest pain, blood pressure increases/decreases, palpitation, pulse rate increases/decreases) 1 28%, **Allergy** (non-specific allergic reactions, hives, allergic rhinitis, facial swelling and sensitivity) 1 03%, **Special Senses** (conjunctivitis, ear infections, vertigo) 0 94%, **Metabolic-Nutritional** (edema weight gain) 0 60%, **Urinary Tract** (urinary tract infections, renal calculi, urethritis) 0 46%, **Genital Tract** (prostatitis, epididymitis) 0 46%, **Psychiatric** (anxiety, depression, fatigue) 0 28%, **Hematology** (lymphadenopathy, thrombocytopenia) 0 23%, **Endocrine** 0 09%
Patients have been followed for up to 5 years and there has been no change in incidence or severity of reported reactions Additional events reported since marketing include eczema, hypertrichosis, local erythema, pruritus, dry skin/scalp flaking, sexual dysfunction, visual disturbances including decreased visual acuity, exacerbation of hair loss, alopecia

DOSAGE AND ADMINISTRATION
Hair and scalp should be dry before application. 1 mL should be applied to the total affected areas twice daily Total daily dose should not exceed 2 mL. If the fingertips are used to facilitate drug application, wash the hands afterwards

HOW SUPPLIED
60 mL bottle with multiple applicators NDC 0009-3367-05
Caution Federal law prohibits dispensing without a prescription

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The Western Journal of Medicine

(ISSN 0093-0415/USPS 084 480) is published monthly for $30 per year (USA and Canada) by the California Medical Association, 221 Main Street, San Francisco, CA 94105. Second-class postage paid at San Francisco, CA and additional mailing offices.

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EDITED BY DAVID SMITH, MD

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The Western Journal of Medicine

(ISSN 0093-0415/USPS 084 480) is published monthly for $35 per year (USA and Canada) by the California Medical Association, 221 Main Street, San Francisco, CA 94105. Second-class postage paid at San Francisco and additional mailing offices.

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From the Division of Cardiology, Departments of Medicine and Neurology, University of Colorado Health Sciences Center, Denver. Dr Florek is currently with the Gundersen Clinic, La Crosse, Wisconsin, and Dr Triffon is currently with the Scripps Clinic, La Mesa, California.

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3. Data on file, Lilly Research Laboratories.
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5. Am J Gastroenterol 1989;84:769-774.

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Indications and Usage: 1. *Active duodenal ulcer*—for up to eight weeks of treatment. Most patients heal within four weeks.

2. *Maintenance therapy*—for healed duodenal ulcer patients at a reduced dosage of 150 mg h.s. The consequences of therapy with Axid for longer than one year are not known.

Contraindication: Known hypersensitivity to the drug. Use with caution in patients with hypersensitivity to other H_2-receptor antagonists.

Precautions: *General*—1. Symptomatic response to nizatidine therapy does not preclude the presence of gastric malignancy.

2. Dosage should be reduced in patients with moderate to severe renal insufficiency.

3. In patients with normal renal function and uncomplicated hepatic dysfunction, the disposition of nizatidine is similar to that in normal subjects.

Laboratory Tests—False-positive tests for urobilinogen with Multistix® may occur during therapy.

Drug Interactions—No interactions have been observed with theophylline, chlordiazepoxide, lorazepam, lidocaine, phenytoin, and warfarin. Axid does not inhibit the cytochrome P-450 enzyme system; therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. In patients given very high doses (3,900 mg) of aspirin daily, increased serum salicylate levels were seen when nizatidine, 150 mg b.i.d., was administered concurrently.

Carcinogenesis, Mutagenesis, Impairment of Fertility—A two-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose-related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a two-year study in mice, there was no evidence of a carcinogenic effect in male mice, although hyperplastic nodules of the liver were increased in the high-dose males as compared with placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups. The rate of hepatic carcinoma in the high-dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement as compared with concurrent controls and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery are not considered evidence of a carcinogenic potential for Axid.

Axid was not mutagenic in a battery of tests pertormed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, mouse lymphoma assay, chromosome aberration tests, and a micronucleus test.

In a two-generation, perinatal and postnatal fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

Pregnancy—Teratogenic Effects—Pregnancy Category C—Oral reproduction studies in rats at doses up to 300 times the human dose and in Dutch Belted rabbits at doses up to 55 times the human dose revealed no evidence of impaired fertility or teratogenic effect; but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights. On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in one fetus, and at 50 mg/kg, it produced ventricular anomaly, distended abdomen, spina bifida, hydrocephaly, and enlarged heart in one fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers—Studies in lactating women have shown that 0.1% of an oral dose is secreted in human milk in proportion to plasma concentrations. Because of growth depression in pups reared by treated lactating rats, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

Pediatric Use—Safety and effectiveness in children have not been established.

Use in Elderly Patients—Healing rates in elderly patients were similar to those in younger age groups as were the rates of adverse events and laboratory test abnormalities. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

Adverse Reactions: Clinical trials of varying durations included almost 5,000 patients. Among the more common adverse events in domestic placebo-controlled trials of over 1,900 nizatidine patients and over 1,300 on placebo, sweating (1% vs 0.2%), urticaria (0.5% vs <0.01%), and somnolence (2.4% vs 1.3%) were significantly more common with nizatidine. It was not possible to determine whether a variety of less common events was due to the drug.

Hepatic—Hepatocellular injury (elevated liver enzyme tests or alkaline phosphatase) possibly or probably related to nizatidine occurred in some patients. In some cases, there was marked elevation (>500 IU/L) in SGOT or SGPT and, in a single instance, SGPT was >2,000 IU/L. The incidence of elevated liver enzymes overall and elevations of up to three times the upper limit of normal, however, did not significantly differ from that in placebo patients. Hepatitis and jaundice have been reported. All abnormalities were reversible after discontinuation of Axid.

Cardiovascular—In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in two individuals administered Axid and in three untreated subjects.

CNS—Rare cases of reversible mental confusion have been reported.

Endocrine—Clinical pharmacology studies and controlled clinical trials showed no evidence of antiandrogenic activity due to nizatidine. Impotence and decreased libido were reported with equal frequency by patients on nizatidine and those on placebo. Gynecomastia has been reported rarely.

Hematologic—Fatal thrombocytopenia was reported in a patient treated with nizatidine and another H_2-receptor antagonist. This patient had previously experienced thrombocytopenia while taking other drugs. Rare cases of thrombocytopenic purpura have been reported.

Integumental—Sweating and urticaria were reported significantly more frequently in nizatidine- than in placebo-treated patients. Rash and exfoliative dermatitis were also reported.

Hypersensitivity—As with other H_2-receptor antagonists, rare cases of anaphylaxis following nizatidine administration have been reported. Because cross-sensitivity among this class has been observed, H_2-receptor antagonists should not be administered to those with a history of hypersensitivity to these agents. Rare episodes of hypersensitivity reactions (eg, bronchospasm, laryngeal edema, rash, and eosinophilia) have been reported.

Other—Hyperuricemia unassociated with gout or nephrolithiasis was reported. Eosinophilia, fever, and nausea related to nizatidine have been reported.

Overdosage: Overdoses of Axid have been reported rarely. If overdosage occurs, activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. Renal dialysis for four to six hours increased plasma clearance by approximately 84%.

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Additional information available to the profession on request.

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62 **Clozapine—A New and Different Neuroleptic**

Discussants: ELLEN HALLER, MD, and RENÉE L. BINDER, MD

Discussions for this section of the journal are usually selected from presentations made at the weekly staff conference in the Department of Medicine at the University of California, San Francisco (UCSF). This conference, however, was presented by the UCSF Department of Psychiatry. Taken from a transcription, it was edited by Homer A. Boushey, MD, Professor of Medicine, and Nathan M. Bass, MD, PhD, Associate Professor of Medicine, under the direction of Lloyd H. Smith, Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine.

65 **Extracorporeal Shock Wave Lithotripsy of Urinary Calculi—Theory, Efficacy, and Adverse Effects**

JAMES M. KELLEY

The author is a third-year medical student at the University of Arizona College of Medicine, Tucson. This paper was chosen as the winner of The Western Journal of Medicine*'s 1990 Medical Student Writing Competition.*

EPITOMES—IMPORTANT ADVANCES IN CLINICAL MEDICINE

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76 **Ignorance—Inevitable but Invigorating**

ROBERT H. MOSER, MD

From the Department of Medical Affairs, The NutraSweet Company, Deerfield, Illinois.

77 **Challenges From the Environment**

ABBA I. TERR, MD

Dr Terr is an allergist in private practice in San Francisco.

78 **Endometrial Cancer—The High-Risk Early-Stage Patient**

C. PAUL MORROW, MD

From the Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, University of Southern California School of Medicine, Los Angeles.

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Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalmic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon® is indicated as a sympathicolytic and mydriatric. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.[1,2] Also dizziness, headache, skin flushing reported when used orally.[1,3]

Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.[1,3,4] 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to ½ tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.[3]

How Supplied: Oral tablets of Yocon® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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GABRIEL GARCIA, MD; ANTONINA SMEDILE, MD; KATHERINE F. BERGMANN, PhD; JOHN L. GERIN, PhD; PETER B. GREGORY, MD; THOMAS C. MERIGAN, MD; and WILLIAM S. ROBINSON, MD

From the Department of Medicine, Division of Gastroenterology, Stanford University School of Medicine, Stanford, California, and the Division of Molecular Virology and Immunology, Georgetown School of Medicine, Rockville, Maryland.

82 **Disseminated *Pneumocystis carinii* in a Patient Receiving Aerosolized Pentamidine Prophylaxis**

STEPHEN M. BERMAN, MD, PhD; BEENA SHAH, MD; FREDERIC A. WYLE, MD; MARIA DACOSTA-IYER, MD; and D. MICHAEL McRAE, MD

From the Infectious Diseases Section, Medical Service, and Laboratory Service, Veterans Administration Medical Center, Long Beach, California.

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BRUCE W. SPURLOCK, MD

87 **Allergy Screening Tests**

VINCENT A. MARINKOVICH, MD

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88 **Physician Payment Reform**

MARK C. LEVINE, MD

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89 **A Young Man With Recurrent Pulmonary Infections**

CARLOS A. CAMARGO, Jr, MPH; GEORGE B. MYCHALISKA, MS; and GORDON GAMSU, MD

Mr Camargo is a fourth-year medical student and Mr Mychaliska is a third-year medical student at the University of California, San Francisco (UCSF), School of Medicine. Dr Gamsu is with the Department of Radiology, UCSF.

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MARK PACKER

Mr Packer is a fourth-year medical student at the University of California, Davis, School of Medicine.

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★ Official Journal of the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

★ Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.

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ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

September 7-9—**Geriatrics of the 90s: Clinical Management of the Elderly Patient.** Symposia Medicus at The Princess Resort, Scottsdale. Fri-Sun. Contact: Jim Goodrich, (415) 935-7889.

September 8-9—**Pulmonary and Infectious Diseases.** Mayo Clinic-Scottsdale at Los Abrigados Resort, Sedona. Sat-Sun. Contact: Jodi Lee Smith, (602) 391-8300.

October 5-6—**Cancer Reviews.** Mayo Clinic-Scottsdale at Orange Tree Golf and Conference Center, Scottsdale. Fri-Sat. Contact: Jodi Lee Smith, (602) 391-8300.

October 19-20—**Common Clinical Problems in the Elderly and Nursing Home Care.** Arizona Geriatrics Society at Arizona Golf Resort and Conference Center, Mesa. Fri-Sat. Contact: Marian Richardson, (602) 974-4212.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Jodi Lee Smith, Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 391-8300.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6707.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 541-0900. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ALLERGY

September 15—**Diagnostic and Therapeutic Choices in Allergy and Immunology.** Los Angeles Society of Allergy and Clinical Immunology at Regent Beverly Wilshire Hotel, Beverly Hills. Sat. 8 hrs. Contact: Sherri Cartwright, 1626 N Wilcox, No 557, Hollywood 90028. (818) 240-6735.

ANESTHESIOLOGY

September 8-9—**Case Conference in Anesthesia.** California Society of Anesthesiologists at Lake Tahoe, California. Sat-Sun. 20 hrs. $175. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

October 28-November 2—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Westin Maui Hotel, Kaanapali Beach, Hawaii. Sun-Fri. 20 hrs. $345. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

November 16-18—**Anesthesiology Update: 1990.** UCD at Monterey Plaza. Fri-Sun. Contact: UCD.

CARDIOLOGY

August 3-4—**Series II—Arrhythmias: Interpretation, Diagnosis, and Management.** Medical Education Resources at Disneyland Hotel, Anaheim. Fri-Sat. 11 hrs. $295. Contact: MER, 1500 W Canal Court, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

August 17-18—**Series IV—Cardiac Wellness and Rehabilitation.** Medical Education Resources at Doubletree Inn, Monterey. Fri-Sat. 11 hrs. $295. Contact: MER, 1500 W Canal Court, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

September 14-15—**Series I—Coronary Heart Disease Update.** Medical Education Resources at Las Vegas Hilton. Fri-Sat. 11 hrs. $295. Contact: MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80123. (800) 421-3756.

October 13—**Myocardial Infarction: Contemporary Management.** UCD at Hyatt Regency, Sacramento. Sat. Contact: UCD.

October 19-20—**Series I—Coronary Heart Disease Update.** Medical Education Resources at Grand Hyatt Union Square, San Francisco. Fri-Sat. 11 hrs. $295. Contact: MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80123. (800) 421-3756.

October 26-27—**Series II—Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Las Vegas Hilton. Fri-Sat. 12 hrs. $275. Contact: MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80123. (800) 421-3756.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact. Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Avenue, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7186.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

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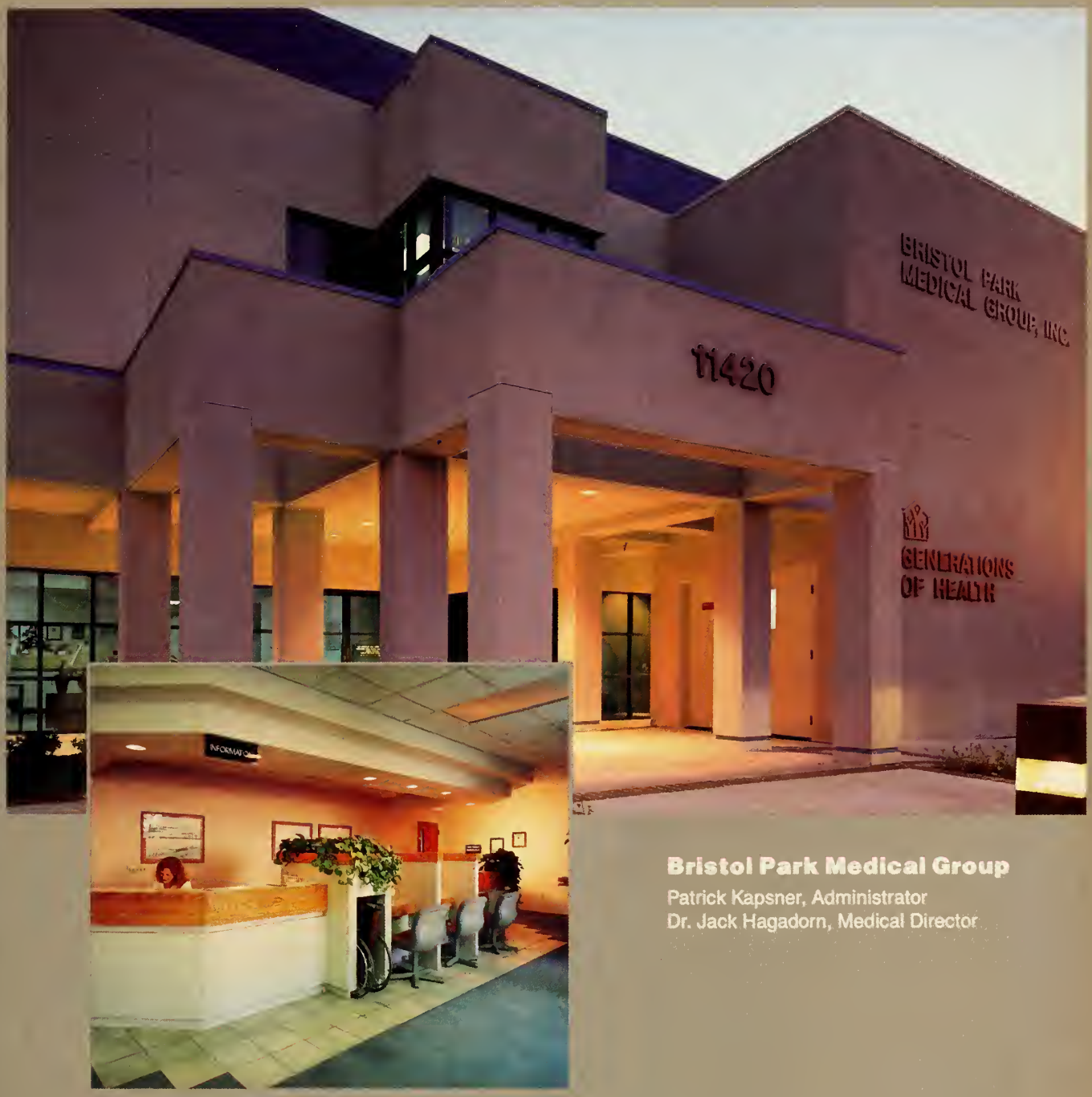

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December 1—**8th Annual Reider Laser Center: International Pulmonary Symposium on Brachytherapy and Argon and ND: YAG Lasers with ND: YAG Laser Workshop.** Memorial/UCI Center for Health Education at Long Beach. Sat. Contact: UCI.

DERMATOLOGY

August 3-4—**Southwestern Regional Cryostat and Microscopically Controlled Surgical Workshop.** UCSD. 15 hrs. Contact: Daniel E. Gormley, MD, 412 W Carroll, Ste 207, Glendora 91740. (818) 963-7684.

August 16-19—**Advanced Seminars in Dermatology.** UCSD at Catamaran Resort Hotel, San Diego. Thurs-Sun. Contact: UCSD.

October 20-21—**The Skin from A to Z.** UCSF at Laurel Heights Campus, San Francisco. Sat-Sun. Contact: UCSF.

EMERGENCY MEDICINE

August 1-5—**Wilderness Medicine: '90.** American College of Emergency Physicians at Squaw Valley Lake Tahoe, Nevada. Wed-Sun. 22 hrs. $395. Contact: Eugene Allred, MD, PO Box 321, Yreka 96097. (800) 888-5632.

August 20-24—**Emergency Medicine Symposium II: Trauma and Surgery.** UCSD at La Jolla Marriott. Mon-Fri. 32 hrs. $450. Contact: UCSD.

October 11-13—**Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Hyatt Union Square. Thurs-Sat. 15 hrs. $375. Contact: UCSF.

October 22-26—**Postgraduate Institute for Primary Care and Emergency Physicians Symposium I: Cardiology, Pulmonary, Neurology.** Mon-Fri. 32 hrs. $450. Contact: UCSD.

October 29-November 3—**Topics in Emergency Medicine.** UCSF at Holiday Inn Golden Gate. Mon-Sat. 32 hrs. $460. Contact: UCSF.

November 12-16—**Emergency Medicine Symposium III: Pediatrics, OB/GYN, Legal Aspects, Dermatology.** UCSD at Hyatt Regency, La Jolla. Mon-Fri. 32 hrs. $450. Contact: UCSD.

December 10-14—**Emergency Medicine Symposium II: Trauma and Surgery.** UCSD at La Jolla Marriott. Mon-Fri. 32 hrs. $485. Contact: UCSD.

FAMILY PRACTICE/PRIMARY CARE

July 19-21—**Rheumatology and Arthritis: A Conference for Primary Care Physicians.** Sharp Memorial Hospital at Catamaran Resort Hotel, San Diego. Thurs-Sat. 13 hrs. $250. Contact: Sharp Memorial Hospital, 7901 Frost St, San Diego 92123. (619) 541-3525.

August 24-26—**3rd Coronado Summer Conference on Primary Care Medicine: A Practical Approach.** Scripps Clinic and Research Foundation at Le Meridien Hotel Coronado Island, San Diego. Fri-Sun. 15 hrs. $275. Contact: Heidi Jurgens, Box 400S, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

October 3-5—**Primary Care Medicine: Principles and Practice.** UCSF at Holiday Inn Golden Gateway, San Francisco. Wed-Fri. 19 hrs. $425. Contact: UCSF.

INTERNAL MEDICINE

August 19-24—**New Advances in Internal Medicine.** UCD at Hyatt Regency, Monterey. Sun-Fri. Contact: UCD.

September 13-15—**3rd Annual New Advances in Common Neurologic Disorders.** UCSD at Catamaran Resort Hotel, San Diego. Thurs-Sat. 14 hrs. $300. Contact: Meeting Management, 5665 Oberlin Dr, Ste 110, San Diego 92121. (619) 453-6222.

September 14-16—**Gastroenterology.** UCSF at San Francisco Hilton and Towers. Fri-Sun. 17 hrs. $415. Contact: UCSF.

October 18-20—**Breast Cancer Seminar.** Memorial/UCI Center for Health Education at Stouffer Hotel, Palm Springs. Thurs-Sat. Contact: UCI.

October 22-24—**14th Annual Cancer Symposium.** Scripps Memorial Hospital at Sheraton Harbor Island Hotel, San Diego. Mon-Wed. 20 hrs. $390. Contact: Meeting Management, 5665 Oberlin Dr, Ste 110, San Diego 92121. (619) 453-6222.

October 20—**Lipids Conference.** UCD at Sheraton Sunrise, Sacramento. Sat. Contact: UCD.

November 9-10—**Metabolic Control of Diabetes.** Memorial/UCI Center for Health Education at Westin South Coast Plaza, Costa Mesa. Fri-Sat. Contact: UCI.

November 30-December 1—**Northern California Internal Medicine Update.** UCD at Hilton Inn. Fri-Sat. Contact: UCD.

OB/GYN

August 17-19—**3rd Annual Perinatal Review.** Memorial/UCI Center for Health Education at Four Seasons Hotel, Newport Beach. Fri-Sun. Contact: UCI.

August 21-25—**8th Annual Controversies in OB/GYN.** Memorial/UCI Center for Health Education at Mauna Kea, Hawaii. Tues-Sat. Contact: UCI.

November 8-11—**Current Issues in Perinatal Medicine.** Memorial/UCI Center for Health Education at Marriott's Rancho Las Palmas Resort, Palm Springs. Thurs-Sun. Contact: UCI.

November 11-17—**13th Annual Review Course in Clinical OB/GYN and/or Gynecological Histopathology.** Memorial/UCI Center for Health Education at Westin South Coast Plaza, Costa Mesa. 1 week. Contact: UCI.

November 29-December 1—**Nebraska OB/GYN Society Meeting.** Nebraska OB/GYN at Las Vegas, Nevada. Thurs-Sat. Contact: University of Nebraska Medical Center, 42nd and Dewey Ave, Omaha, NE 68105-1065. (402) 559-4152.

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July 23-27—**4th Annual Sports Medicine.** UCSD at San Diego Princess. Mon-Fri. 22 hrs. $350. Contact: UCSD.

October 2-7—**Sports Medicine Update.** Memorial/UCI Center for Health Education at Mauna Kea Hotel, Hawaii. Tues-Sun. Contact: UCI.

October 8-19—**Occupational and Environmental Medicine Session II.** UCSF at Cathedral Hill Hotel, San Francisco. 1½ weeks. 80 hours. $1,200. Contact: UCSF.

October 15-19—**Current Topics in Occupational Medicine.** UCSF at Cathedral Hill Hotel, San Francisco. Mon-Fri. 40 hrs. $600. Contact: UCSF.

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August 26-30—**Ophthalmology Update: 1990.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Thurs. Contact: UCD.

August 26-29—**External Disease: Diagnosis and Management for the 1990's.** UCD at Hyatt Regency Lake Tahoe, Incline Village, Nevada. Sun-Wed. 13 hrs. $350. Contact: UCD.

September 14-16—**Uveitis/Retinal Frontiers: Diagnostic, Medical and Surgical Approaches to Uveitis.** UCSF at Carmel Valley Ranch Resort. Wed-Fri. Contact: UCSF.

November 30-December 2—**American Academy of Ophthalmology Regional Update Course.** American Academy of Ophthalmology at Los Angeles. Fri-Sun. Contact: Gary Holland, (213) 825-9508.

ORTHOPAEDICS

October 4-6—**Orthopaedic Update.** UCSD at Hyatt La Jolla. Thurs-Sat. Contact: Pat Curl, PO Box 33185, San Diego 92103. (619) 692-9115.

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October 4-6—**International Symposium on Medical Virology.** UCI at Four Seasons Hotel, Newport Beach. Thurs-Sat. Contact: Luis M. de la Maza, (714) 634-6868.

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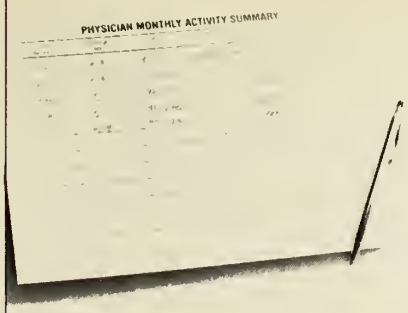
October 19—**Fine Needle Aspiration Tutorials.** UCSF. Fri. 7 hrs. Contact: UCSF.

(Continued on Page 94)



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Biomedical Science

Medical Ignorance, AIDS-Kaposi's Sarcoma Complex, and the Lymphatic System

MARLYS H. WITTE, MD; CHARLES L. WITTE, MD; *and* DENNIS L. WAY, *Tucson*

Presented at the Plenary Session, Western Association of Physicians, Carmel, California, February, 6, 1990.

In the introduction to the *Cecil Textbook of Medicine*, Lewis Thomas, whose prize-winning collections of essays on biology have delighted both the medical profession and the lay public, gives a unique prescription for what ails medical education. Since, he reasons, the greatest single achievement of science in this most scientifically productive of centuries is the recognition that we know very little about nature and understand even less, he wishes there were "some formal courses in medical school on Medical Ignorance; textbooks as well, although they would have to be very heavy volumes. We have a long way to go."[1(pxliii)] Ironically, celebrated medical triumphs flowing from the information and technology explosion often do reveal most notably our ignorance: that which we don't—but need to—understand. The Curriculum on Medical Ignorance (Figure 1, top), begun in 1985 at the University of Arizona College of Medicine, aims to help students recognize and deal with this vast intimidating world of nonknowledge composed of the things we know we don't know, the things we don't know we don't know, and the things we think we know but don't.[2-4] Our goals (Table 1) are to enlarge the understanding of the shifting domains of medical knowledge, uncertainty, ambiguity, and the unknown and how one decade's facts become the next's follies and vice versa; improve skills in working within this context; and develop the needed attitudes to recognize and deal with ignorance. Activities (Table 1) include a summer institute of full-time hands-on basic and clinical research and workshops largely for first- and second-year students; a clinical elective, "Seminars and Clinics on Medical Ignorance," for third- and fourth-year medical students; and a seminar series featuring visiting professors of ignorance, that is, "distinguished ignoramuses" who are not only leading experts in their discipline but also have keen insight into the great unknowns and are willing to admit their limitations.

The central thrust of these experiences is the reverse of most medical curricula—that is, learning how to question, rather than how to answer, whether about the basic biology of an illness (type 1 ignorance questions); the diagnosis, prognosis, and treatment of specific diseases (type 2 ignorance questions); or related socioeconomic, legal, and ethical issues (type 3 ignorance questions). The House of Ignorance (Figure 1, bottom)—*La Residencia del Incognitó*—across the street from the University of Arizona Cancer Center provides a congenial book-free atmosphere for unknowers, including students, mentors, and visiting professors, who gather together and explore the cutting edge of the unknown. Students are graded not by short-answer tests, but primarily by the progression of their questions, which they record serially in weekly "ignorance logs" as they explore, analyze, discuss, carry out research, and practice making clinical decisions where lives may hang in the balance. Student evaluations praise this curriculum for "bringing home how ignorance abounds," "offering time and encouragement to put things into perspective," "reinforcing a thirst for knowledge," "awakening curiosity and enthusiasm dampened by excessive passive learning," and "demonstrating that it takes a lot of effort and knowledge to appreciate ignorance and find the most important questions that aren't, rather than are, answered in a field." Thus, some of our best students, by dint of hard work, probing intellect, and resourcefulness, are leaving the University of

TABLE 1.—*Goals and Methods of the Curriculum on Medical Ignorance at the University of Arizona College of Medicine*

Curriculum Goals	*Activities and Courses*
Gain understanding of the shifting domains of ignorance, uncertainty, and the unknown: philosophical and psychological foundations and approaches to learning, questioning, and creating "knowledge"; history and development of selected ideas and methods in basic and clinical medical science; mastery by in-depth multidimensional exploration of selected timely medical topics	Summer Institute on Medical Ignorance Seminars and Clinics on Medical Ignorance Full-time basic and clinical research Questions and questioning exercises Creative thinking exercises Final oral and written reports on selected topics in Medical Ignorance Weekly ignorance logs Visiting professors of Medical Ignorance La Residencia del Incognitó
Improve skills to recognize and deal productively with ignorance, uncertainty, and the unknown: question critically and creatively focus on raising, listening to, analyzing, prioritizing, and answering questions from different points of view; communicate clearly in different media with various audiences; collaborate effectively with different people and other resources	
Reinforce positive attitudes and values of curiosity, optimism, humility, self-confidence, and skepticism	

(Witte MH, Witte CL, Way DL: Medical ignorance, AIDS-Kaposi's sarcoma complex, and the lymphatic system. West J Med 1990 Jul; 153:17-23)

From the Department of Surgery, University of Arizona College of Medicine, Tucson.

This work was supported in part by grants from the American Medical Association Education and Research Foundation, National Institutes of Health (T35-HL07479 and P50-AA08037), Arizona Disease Control Research Commission (Contracts No. 8277-000000-1-1-AT-6625 and -B-7492), and the World Health Organization (Contract No. 870051).

Reprint requests to Marlys H. Witte, MD, Professor of Surgery, University of Arizona College of Medicine, 1501 N Campbell Ave, Tucson, AZ 85724.

ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
HIV = human immunodeficiency virus

Arizona College of Medicine more ignorant than when they entered!

In this discourse, we will present, with the aid of only one Western blot, a personal odyssey in medical ignorance stretching over the past several decades from the ghettoes of St Louis to the golden temples of India, exploring swollen limbs and swollen bodies through the eyes of lymphologist-lymphomaniacs, coursing back and forth from blood to lymph to gain a glimmer of understanding about an odd group of disfiguring, disabling, and, at times, life-threatening disturbances of the lymphatic system (Figure 2). An array of fragmentary ideas, false starts, and some chance discoveries also happened along the way.

Our story begins more than 20 years ago in September 1968 in the now-defunct St Louis (Missouri) City Hospital, where we first encountered a teenager with brawny swollen legs and elephantine genitalia of several months' duration (Figure 3),[5] which he traced back to several heterosexual encounters. He had not traveled outside the St Louis area, nor had he received blood transfusions or abused drugs. Dorsal pedal lymphangiography displayed complete lymphatic obstruction at both groins with dermal backflow of the oil contrast medium; an excised inguinal lymph node showed marked fibrosis. Over the ensuing 15 months, his clinical course was progressively downhill with intermittent fever, ascending body wall lymphedema, recurrent bilateral pleural effusions, and a 23-kg (50-lb) weight loss. Chlamydial microorganisms were repeatedly identified in blood and body fluids, and hypoproteinemia and pronounced peripheral lymphocytopenia progressively worsened despite aggressive antimicrobial therapy. At autopsy, not only was a solitary purplish cutaneous nodule of Kaposi's sarcoma visible on the medial aspect of his right thigh, but much of the edematous fibrotic soft tissue throughout the body, including the chronically inflamed anorectum,

Figure 1.—The top photo is of an instructor's guide for teaching the Curriculum on Medical Ignorance, and the bottom photo shows the House of Ignorance *(La Residencia del Incognito)*, dedicated to students and faculty exploring medical unknowns together.

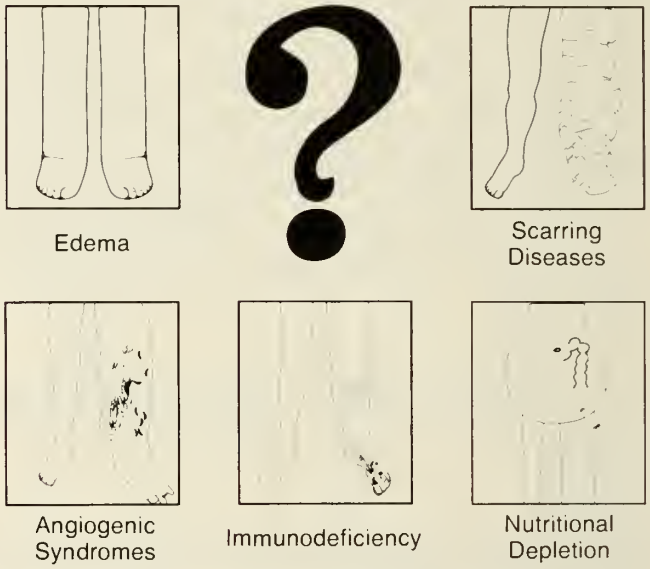

Figure 2.—There is a puzzling constellation of findings in disorders of the lymphatic system.

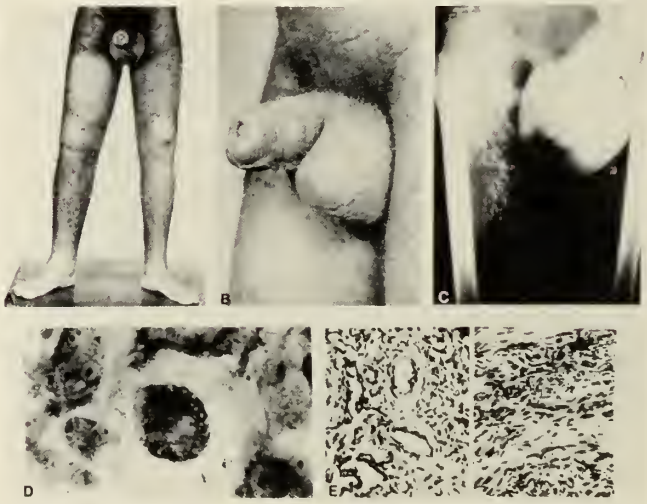

Figure 3.—The photos illustrate case study in medical ignorance #1: The initial appearance **(A,B)** of a 15-year-old adolescent boy with pronounced swelling of the penis, scrotum, and lower extremities. Genitalia show brawny edema and minute cystic swellings representing lymphatic vesicles on the penis and scrotum. Conventional lymphography **(C)** reveals obstruction of leg lymphatics at the groin with dermal backflow. A photomicrograph **(D)** of irradiated McCoy tissue culture of ascitic fluid obtained at postmortem shows "initial bodies" (dark cytoplasmic blebs), an intracellular phase of *Chlamydia* species (original magnification × 750). Photomicrographs **(E)** of groin subcutaneous tissue show abnormal lymphatics lined by atypical endothelial cells with pleomorphism and hyperchromatic nuclei (hematoxylin and eosin, × 416). Questions abound (see text). (From Elvin-Lewis et al,[5] reprinted with permission.)

was infiltrated with a vascular malignant lesion variously interpreted as Kaposi's sarcoma or lymphangiosarcoma. Lymph nodes, spleen, bone marrow, and thymus exhibited profound lymphocytic depletion with few precursors, extensive fibrosis, and scattered Kaposi's lesions.

At that time, we were at a loss to put a name on this patient's ailment, nor could we find previous reports of a similar constellation of findings—swelling, scarring, wasting, immunodeficiency, and uncontrolled angiogenesis. As busy clinicians and investigators, this was not our first brush with medical ignorance, nor would it be our last, but it was the one that was to stick most vividly over the years in the comfortable but almost forgotten "attic" of our collective brains. This "attic of the brain" Thomas views as the

> darkest and strangest part of the building, reachable only by placing a stepladder beneath the trapdoor and filled with unidentifiable articles too important to be thrown out with the trash but no longer suitable to have at hand. . . . all the things deposited in it became, one by one, lost to consciousness. But they were still there . . . safely and comfortably stored in the tissues of the house . . . [a] place for functionless, untidy, inexplicable notions, [the] dark comfortable parts of the mind to hide away the things we'd like to keep but at the same time forget.[6(pp138,140)]

In 1973 when we published a detailed report of this case in the journal *Lymphology*,[5] the group of physicians who had cared for the patient had gone their separate ways, our team to the new University of Arizona College of Medicine. We continued investigations, delving into the mysteries of body swellings from high-output failure of the lymph circulation where an overworked lymphatic system, despite accelerated flow, still fails to drain fully excess tissue fluid arising from an imbalance in the Starling hydrostatic and oncotic forces at the capillary-tissue interface.[7,8] For example, patients with portal hypertension from hepatic cirrhosis, whether or not ascites is present, uniformly show staggering increases (sixfold or more) in central thoracic duct lymph flow. How do some cirrhotic patients turn into frogs with lymph hearts pumping back many times their plasma volume daily but still not enough in some to keep pace with lymph formation, so that ascitic fluid accumulates with disastrous consequences? Yet treatment aimed at reducing excessive splanchnic lymph formation by portal decompression through a portasystemic shunt, or at accelerating lymph absorption through a megalymphatic peritoneovenous LeVeen shunt, may restore the balance between the formation and absorption of lymph, and ascites recedes. But all swellings are not alike. In contrast to the pitting, water-logged tissues of the high-flowing lymph states from venous hypertension, the high-protein brawny edemas from low-output failure of the lymph circulation, as in lymphatic blockade, provoke progressive tissue fibrosis, intense neovascularization, and fat deposition, as exemplified by elephantine limbs with their striking resemblance to a cirrhotic liver and the leonine facies of lepromatous leprosy.[7,8] And why is lymphedema so hard to undo? We begin to envision a more encompassing blood-lymph circulatory loop transporting, or, in disease, failing to transport, not only liquid and small solutes but also macromolecules, particles, and lymphoid cells through tissues, lymphatics, and lymph nodes back to the bloodstream and around again and again.

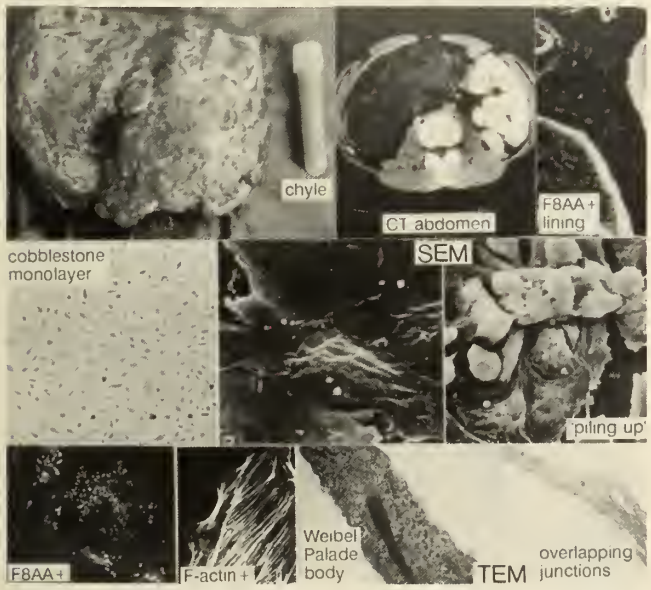

Figure 4.—A lymphatic endothelial cell line, CH3, derived from giant recurrent retroperitoneal lymphangioma raises questions about the link between lymphatic malformations and neoplasia. The top row shows, **left to right**, an operative specimen with chylous contents, a radiolucent mass on abdominal computed tomography (CT), and cyst lining immunofluorescence for endothelial marker, factor VIII-associated (F8AA+) antigen. CH3 displays cobblestone morphologic features **(middle row, left)** and on scanning electron microscopy (SEM; **middle** [original magnification × 471] **and right** [× 114]) is composed of polygonal cells, in some areas "piling up," that are positive for factor VIII-associated antigen and F-actin **(bottom row, 2 left photos** [× 80 and × 266, respectively]**)**. On transmission electron microscopy (TEM), the polygonal cells contain Weibel-Palade bodies and show lymphatic-like overlapping intercellular junctions **(2 right photos** [× 6300 and × 1900, respectively]**)** (from Way et al,[13] reprinted and made into composite with permission).

Time passes rapidly, and it is already 1981. Simultaneously on the East and West coasts, a perplexing new clinical syndrome[9,10] is attacking young gay men, causing profound immunodeficiency, rare opportunistic infections, and that same unusual skin cancer of our patient, namely, Kaposi's sarcoma. The striking resemblance of this new acquired immunodeficiency syndrome to that of our St Louis patient from 1968 prompts us (M.H.W., C.L.W.) to write a letter in 1984 to the *Journal of the American Medical Association*.[11]

New questions arising in the clinic and laboratory concerning a constellation of overlapping findings in lymphologic syndromes once again distract our attention from the strange case described here. Intrigued by the isolation of long-lived lymphatic endothelial cell lines from lymphatic malformations and tumors such as a massive, rapidly growing, cervicomediastinal cystic hygroma associated with diffuse bony lymphangiomatosis[12] and a giant, recurrent, cavernous, chyle-filled retroperitoneal lymphangioma (Figure 4),[13] we begin to question the fine line between congenital anomalies and true vascular neoplasia and between benign and malignant growth. A proliferation of both lymphatics and blood vessels, that is, lymphangiogenesis and hemangiogenesis, and even the formation of vascular tumors (angiotumorigenesis) seem to play a central role in syndromes of lymph stasis (Figure 5).[14,15] This angiogenic process is often preceded or accompanied by fibrosis, lipid deposition, recurrent opportunistic infections, and impaired immunity, which is limited to the lymphedematous areas and related in part to locally defective clearance and antigen-processing mechanisms. Furthermore, reduced circulating T-helper lymphocytes in conjunction with lymph nodal and thymic atrophy, diffuse fibrosis, vascular transformation, and malignant lymphomas are prominent features of various lymphedema and chylous syndromes. Rarely, as after radical mastectomy, a chronically lymphedematous extremity is the site of a highly aggressive malignant vascular neoplasm, the so-called Stewart-Treves syndrome.[16] Indeed, we initially labeled our patient's vascular tumor an "angiosarcoma," and he represents the purest personification of this entire conceptual scheme, showing not only "local acquired

immunodeficiency syndrome (AIDS)" from uncontrolled lymph stasis in a single limb but also the systemic manifestations in macrocosm.

By now the human immunodeficiency virus (HIV) has been isolated from patients with AIDS, and specific serum tests have become available. To our surprise, we identify circulating antibodies to nine of nine HIV type 1 antigens as well as specific retroviral protein in specimens of our patient's body fluids and tissues frozen in ignorance for nearly 20 years (Figure 6).[17]

Although we had forged a curious biologic link to the past, its meaning was unclear and troubling. Had AIDS actually been around a long time, perhaps even millennia, and maybe did not arise in Africa but emerged as an epidemic and ultimately a pandemic because of some bizarre environmental coincidence? And, would our patient have been better off today with all that we have come to know about this dread syndrome? Unfortunately, no. His disease probably would have been just as rapidly fatal now as in our primitive bewilderment back then, highlighting once again how much ignorance surrounds the explosive core of medical information and biotechnology.

Whereas a Chicago *Tribune* headline hails these findings as "shaking theories of AIDS origin" (J. Crewdson, Chicago *Tribune*, October 25, 1987, p1), this patient's case also exemplifies the interconnectedness of the lymphatic system's four components—lymph, lymphatic vessels, lymph nodes, and lymphocytes—and how closely linked the unhinging of the blood-lymph loop of fluid, macromolecules, and migrating cells is to the processes of swelling, scarring, wasting, immunodeficiency, and angiogenesis.

How, then, can these concepts help to delineate the approach to treatment of these lymphologic syndromes (Figure 7)? First, edema arises when the circulation of tissue fluid or lymph fails, whether in cases of high- or low-output imbalance. When macromolecular movement is also impaired, as in long-standing high-protein lymphedemas, scarring disorders appear. As the migration of lymphoid and other mobile cell populations—particularly the antigen-presenting complex—through tissues, lymphatics, and interposed lymph nodes becomes restricted or disordered, or, alternatively, when lymph is either sequestered internally or lost directly to the outside, immunodeficiency and nutritional depletion syndromes develop. Exuberant angiogenesis and even angiotumorigenesis of lymphatics, blood vessels, or both often accompany or may precede these other abnormalities, presenting as benign or malignant vascular tumors. Lymphatic disturbances of widely different etiologies—genetic, congenital, and acquired—may be localized to a single limb or internal organ, or may involve the whole body (Figure 8).[18] Animal counterparts are also found in nature or can be induced experimentally. When a disorder of the blood-lymph loop is suspected, a comprehensive rational workup can be carried out at the bedside, in the imaging suite, operating room, and laboratory (Figure 9).[19] Using time-honored tools updated to the modern era of molecular biology, lymphologists visualize, sample, analyze, and thereby characterize the disorder. In vivo, lymphatics and nodes are imaged directly by vital dye injection and oil-contrast lymphography or noninvasively by magnetic resonance imaging, fluorescent videomicroscopy, in-

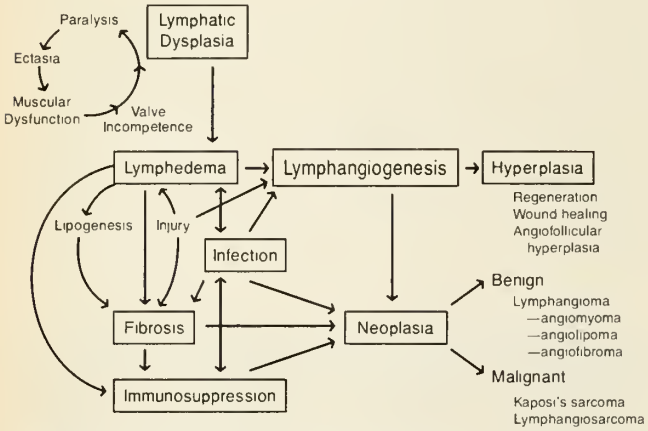

Figure 5.—The diagram illustrates some poorly understood links between lymphangiogenesis and disorders of the lymphatic system characterized by lymph stasis. See text for details (from Witte and Witte,[14] reprinted with permission).

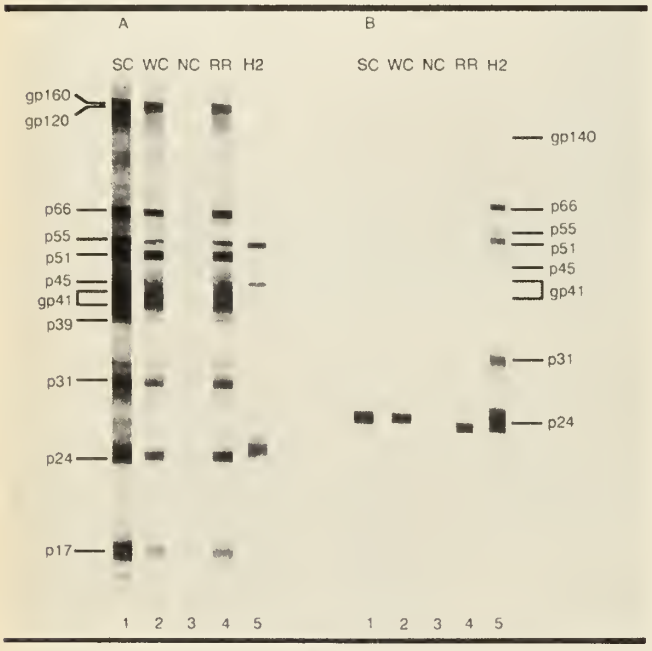

Figure 6.—Western blot reactivity against human immunodeficiency virus (HIV) proteins occurs in serum from a 15-year-old boy initially seen in 1968: panel A shows reactivity against HIV-1 protein, panel B shows reactivity against HIV-2 proteins. Lane 1 (SC) indicates strongly reactive HIV-1-positive serum; lane 2 (WC) has weakly reactive HIV-1-positive serum, lane 3 (NC) shows nonreactive control serum, lane 4 (RR) indicates patient's serum (April 16, 1969), and lane 5 (H2) indicates HIV-2-positive serum. This observation raises more questions than it answers (from Garry et al,[17] reprinted with permission [copyright 1988, American Medical Association]).

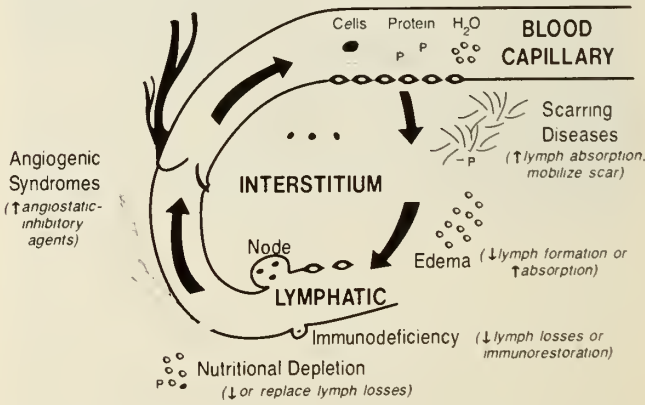

Figure 7.—Characterized, in the face of ignorance, are clinical disorders of the blood-lymph circulatory loop of fluid, small solutes, macromolecules, and cells manifesting as swelling, scarring, immunodeficiency, nutritional depletion, and uncontrolled angiogenesis and angiotumorigenesis. The phrases in italics in parentheses designate therapeutic approaches. See text for details.

direct lymphography, and, most important, by lymphangioscintigraphy after the simple intradermal administration of radioactive protein.[19] Central or regional lymphatics can be cannulated to determine tissue fluid fluxes and lymph and edema fluids analyzed for chemical and cellular constituents. Thus, the anatomic, biochemical, and physiologic disturbance of the blood-lymph loop, whether from lymphatic overload, lymphatic obstruction, or external lymph loss, can be delineated in vivo. In addition, components of the blood-lymph loop can be removed from the body, including lymphatic segments, endothelium, or lymphocytic subpopulations. The tissue or lymphatic microenvironment can then be recreated in vitro, for example, to assess lymphatic contractility or the movement of proteins and lymphocytes across endothelial monolayers or to determine why the "criminal" adult filarial worm (Figure 10), surrounded as in life by human lymphatic endothelium, lymph, and lymphocytes, chooses to dwell in what Indian filariasis researcher Kumaraswamy has called the "police station" of the body, and the "cops do nothing about it."[20]

Figure 8.—These are dramatic examples of the wide variety of genetic, congenital, and acquired disorders in the curious spectrum of lymphologic syndromes: **Top,** left to right, lymphatic filariasis (courtesy S. Jamal), posttraumatic lymphedema, fetal Turner's (XO) syndrome with strangulating cervical cystic hygroma and hydrops. **Bottom, left to right,** Klippel-Trenaunay syndrome, acquired immunodeficiency syndrome-associated Kaposi's sarcoma, and Stewart-Treves lymphangiosarcoma from postmastectomy lymphedema (the last from Stewart et al,[16] reprinted with permission).

Finally, when the disorder of the blood-lymph circulatory loop is pinpointed and characterized in vivo and in vitro, rational therapeutic approaches (Figure 7, italics in parentheses) can be devised and then evaluated by their efficacy in normalizing the blood-lymph loop. For example, in swelling and scarring syndromes, efforts are directed at reducing lymph formation or enhancing lymph absorption and mobilizing scar tissue. Depleted nutritional elements are repleted by halting bulk lymph losses. The deficient cellular or humoral immune system is reconstituted by redirecting migrant lymphoid streams or selectively replacing specific cellular subpopulations. Angiogenic syndromes can be retarded using angiostatic and angioinhibitory drugs. Unfortunately, these rational therapeutic goals are still more often than not unattainable in our present state of ignorance.

The following two kaleidoscopic examples illustrate how the previously hidden lymphatic circulation is finally coming into clinical view to be probed down to the cellular and molecular level and ultimately manipulated. First (Figure 11), in a gay man with AIDS-associated Kaposi's sarcoma, a lesion long thought to derive from lymphatics and to block them,[21,22] lymphangioscintigraphy using technetium Tc 99m-labeled albumin noninvasively visualizes lymph nodal and lymphatic channel abnormalities corresponding to the distribution of cutaneous lesions.[23] A skin biopsy specimen showing prominently dilated lymphatics has yielded on

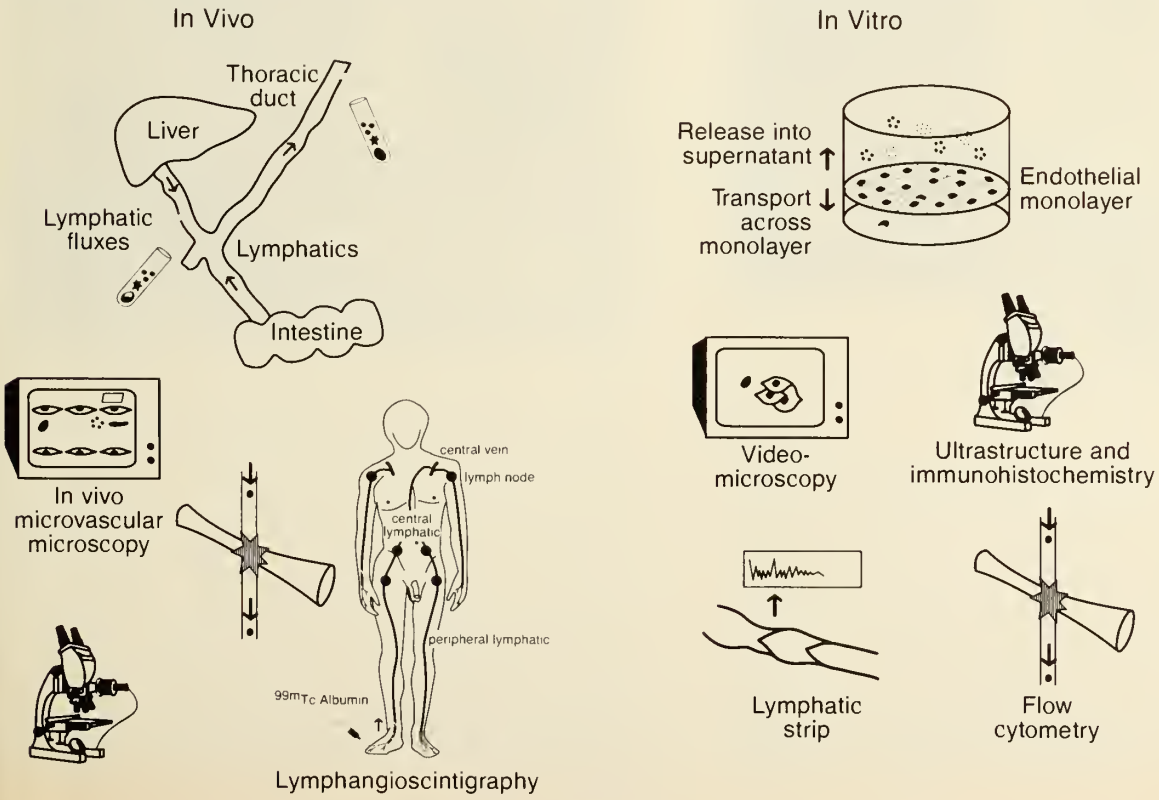

Figure 9.—Some in vivo and in vitro methods to investigate unanswered questions about normal and diseased lymphatic systems are depicted. See text for details.

long-term culture factor VIII-associated, antigen-positive, dendritic spindle-shaped cells resembling both lymphatic and blood vascular endothelium.[24] These cultured AIDS-Kaposi's sarcoma cells are being further characterized by flow cytometry, examined for retroviral and other viral DNA sequences by polymerase chain reaction, used in a hybridoma system to develop specific anti-Kaposi's sarcoma monoclonal antibodies, and subjected to angiostatic and angioinhibitory agents. As ignorance specialists, we wonder, what is the biologic link between the AIDS virus, immune dysregulation, and the lymphatic-derived Kaposi's sarcoma (type 1 ignorance question)? Can the process of angiogenesis and angiotumorigenesis be controlled or reversed with angiostatic-angioinhibitory agents or, alternatively, other modes of lymphatic-targeted therapy (type 2 ignorance question)? What are the societal implications of pursuing these questions, specifically as related to animal rights, human subject research, controlled trials, confidentiality, and cost-benefit ratios (type 3 ignorance question)?

Figure 10.—The intralymphatic environment is recreated to probe ignorance about lymphatic filariasis. **Left,** a scanning electron-microscopic view shows an adult *Brugia malayi* emerging from an infected ferret lymphatic. **Right,** on day 72 of culture, a female *B malayi* is surrounded by microcarrier beads coated with human endothelial cells.

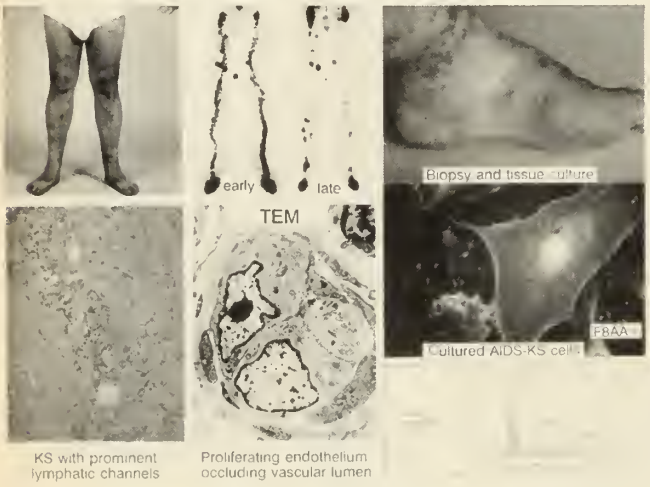

Figure 11.—The photos illustrate case study in medical ignorance #2: **Top row, left,** a 44-year-old gay man with acquired immunodeficiency syndrome (AIDS)-associated Kaposi's sarcoma; **middle,** lymphangioscintigraphy (early, late) shows hyperplastic inguinal lymph nodes on the left and punctate dots of persistent late tracer activity linking deep lymphatic channels to cutaneous lesions; and **right,** biopsy and culture were done of left foot. **Bottom row, left,** the biopsy specimen shows an early Kaposi's sarcoma (KS) lesion with prominent lymphatic channels on histologic examination (hematoxylin and eosin stain, original magnification × 86) and, **middle,** proliferating endothelial cells occluding the vascular lumen on transmission electron microscopy (× 3380) that yielded in long-term culture **(middle right)** distinctive dendritic spindle-shaped cells positive for endothelial marker factor VIII-associated antigen (F8AA+; × 200) and currently undergoing **(bottom right)** further characterization by such methods as DNA cell-cycle kinetics (flow cytometry). Questions abound (see text).

Finally, 20 years after our first case, another 15-year-old (Figure 12) presented to us with a similar picture of progressive, brawny, elephantine genital and lower extremity lymphedema of several years' duration, in this instance preceded and accompanied by recurrent local infection and low circulating T-helper cell counts ($\sim 2 \times 10^6$ per liter [400 per μl]). Lymphangioscintigraphy, confirmed by conventional lymphography, showed lymphatic blockade below the diaphragm with reflux into the pelvis, along with notable hypoplasia of retroperitoneal lymph nodes. Magnetic resonance imaging showed huge lymphatic lakes throughout the left leg and scrotum underlying cutaneous chylous vesicles. At the time of scrotal debulking and construction of a lymphatic venous bypass shunt in the edematous left groin, chyle welled up in the wound. Scrotal tissue showed extensive lymphangiectasia and intense fibrosis on histologic examination and yielded in tissue culture rapidly proliferating lymphatic-like endothelial cells. We ruminate, do these disorders represent a delayed onset of a genetic or congenital disturbance, or are they viral or even retroviral infections detectable by polymerase chain reaction, and does the process begin in lymphatic channels or in lymph nodes (type 1 ignorance questions)? What course of action is best when there is no good "standard" therapy available, are innova-

Figure 12.—The photos illustrate case study in medical ignorance #3: **Top left,** a 15-year-old boy has left leg and scrotal lymphedema associated with recurrent infection and depressed T-helper cell counts. **Top middle,** lymphangioscintigraphy (using human serum albumin labeled with technetium Tc 99m) shows normal lymphatic trunks in the right leg with obstruction below the diaphragm and reflux across the pelvis into the left groin and leg. **Top right,** these findings are confirmed by conventional lymphography (oil-contrast), which also shows hypoplasia of retroperitoneal lymph nodes. **Middle row, left,** the elephantine scrotum is covered by chylous vesicles. **Center,** high-signal-intensity lakes in the genitalia and left leg on magnetic resonance imaging (MRI) correspond to chyle-containing lymphatic cisterns found in the groin wound **(middle row, right)** at the time of scrotal debulking and lymphatic-venous shunting. **Bottom left,** on histologic examination, a specimen of excised scrotal skin and subcutaneous tissue shows myriad dilated lymphatics associated with fibrosis (hematoxylin and eosin stain, original magnification × 50) and, **bottom right,** on tissue culture, yielded rapidly proliferating, lymphatic endothelial-like cells covering microcarrier beads (× 495). Questions abound (see text).

tive operative approaches more prudent than the failed "conservative" standard of care, and how can efficacy be demonstrated (type 2 ignorance questions)? What are the social implications of unraveling the human genome, and how does one gain better understanding of the pathologic process with fetal research banned and the costs of managing rare "orphan" diseases spiraling (type 3 ignorance questions)? Once again, we are confronted with a lymphologic syndrome, manifesting the same constellation of swelling, scarring, immunodeficiency, vigorous angiogenesis, and potential nutritional depletion, to fill the "attic" of the brain and laboratory freezers with ponderables and imponderables for at least another two decades.

Thus, our personal odyssey in medical ignorance and swollen limbs has brought us to unimagined questions at the edge of the unknown. While sharing "late night thoughts" with Lewis Thomas and other renowned unknowers,[25] the uncluttered side of our mind fixes on a concluding insight in the final research report of one of our masterfully "ignorant" medical students:

I learned that if our projects seem easy and we surely understand them, we are not really probing deeply; it is only when we become perplexed by all the new discoveries unfolding before us that we can safely admit to being deep into the realm of research. . . . I truly gained an appreciation (and even a desire) for confusing and unexpected results. Not that I expected the unexpected, but rather I welcomed it when it came, and I eagerly probed to find out why it was unexpected and what it augured for the next set of experiments. . . . I cannot predict where I will be in medicine 20 years from now, but I like that. And I know the lessons of ignorance, creativity, and fortitude engendered in me by these seminars will keep me traveling a meandering path.[26]

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Electrocardiographic Abnormalities in Patients With Myotonic Dystrophy

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In examining the incidence and progression of electrocardiographic abnormalities in 45 patients with myotonic dystrophy, 26 (58%) of whom at entry had at least 1 electrocardiographic abnormality, we found conduction abnormalities in 17 (38%). In 21 patients (47%), new abnormalities developed during follow-up (mean, 4.6 years). The overall incidence of electrocardiographic abnormalities increased to 78%, and the incidence of conduction defects increased to 62%. Second-degree or complete atrioventricular block did not develop in any of the patients. Pseudoinfarction patterns were common at entry and during follow-up and were not correlated with evidence of clinical coronary artery disease. There was no correlation between the presence of electrocardiographic abnormalities and apparent disease severity.

(Florek RC, Triffon DW, Mann DE, et al: Electrocardiographic abnormalities in patients with myotonic dystrophy. West J Med 1990 Jul; 153:24-27)

Myotonic muscular dystrophy is a progressive, genetic, multisystem disease characterized by myotonia, a prolonged contraction of voluntary muscle. Other characteristic manifestations include muscle weakness and atrophy, mental impairment, endocrine dysfunction, cataracts, gastrointestinal abnormalities, testicular atrophy, and frontal baldness.[1] Although clinical cardiac involvement is uncommon, electrocardiographic (ECG) abnormalities have been frequently described[2-10]; they most commonly reflect cardiac conduction system involvement. Data on the progression of ECG abnormalities are limited.[9-11] Previous studies present data from either small series[9,11] or retrospective reviews[2-8] that lack follow-up data.

We determined the prevalence of ECG abnormalities in an unselected group of patients with myotonic dystrophy followed in a neurology clinic, and we prospectively examined the progression of ECG abnormalities during follow-up.

Patients and Methods

In 1979 a registry of all patients with myotonic dystrophy was established at the University of Colorado Health Sciences Center, Denver, Colorado. Entry criteria included myotonia, characteristic muscle involvement (ptosis, nasal speech, orbicularis oculi and oris weakness, neck flexor weakness), or both, and a family history of autosomal-dominant inheritance. At entry and during follow-up, a neurologist took a history and did a physical examination. On follow-up, patients were asked about palpitations, syncope, dyspnea, paroxysmal nocturnal dyspnea, and edema.

For all patients chest x-ray films were taken and standard 12-lead electrocardiograms were recorded at entry and annually during follow-up. Two cardiologists analyzed ECGs independently. First-degree atrioventricular (AV) block, fascicular block, and bundle branch block were diagnosed using standard criteria.[12] Left axis deviation was defined as a frontal plane axis to the left of −30 degrees. Nonspecific interventricular conduction delay was considered present when the QRS complex was longer than 100 milliseconds but shorter than 120 milliseconds. Prolongation of the QRS complex during follow-up was defined as a consistent increase in the QRS duration of at least 20 milliseconds measured in lead V_2. Those Q waves longer than 40 milliseconds and greater than 1 mV in amplitude were considered abnormal. An R/S ratio of greater than 1 in lead V_1 was defined as increased anterior forces.

Electrocardiographic abnormalities were correlated with age and duration of follow-up using an unpaired *t* test and correcting for multiple comparisons.[13] Neuromuscular impairment was assessed by grading for characteristic cranial muscle abnormalities and skeletal muscle strength. Neuromuscular impairment in patients with and without an ECG abnormality was compared with an unpaired *t* test.

Results

Electrocardiographic Abnormalities at Entry

To date, 118 patients from 70 pedigrees have been entered into the registry. The study group consisted of 45 patients (26 men, 19 women; mean age 41 years, range 8 to 63 years) for whom a minimum follow-up of a year was available. Less than one year of follow-up data was available for 73 patients, and they were excluded from analysis. None of the patients received antiarrhythmic therapy during the study period.

Of the 45 patients, 26 (58%) had at least one ECG abnormality on presentation. Left axis deviation was the most frequent abnormality, occurring in 16 patients (36%) (Figure 1). Of these 16 patients, 3 had a QRS axis leftward of −45 degrees and a counterclockwise loop, meeting the criteria for left anterior fascicular block. Left bundle branch block was present in three patients and right bundle branch block in one. Seven patients had a nonspecific interventricular conduction delay. Nine patients (20%) showed first-degree AV block. Abnormal Q waves and increased anterior forces were seen in two and four patients, respectively. A conduction abnormality (first-degree AV block, interventricular conduction delay, fascicular block, or bundle branch block) was present in 17 patients (38%).

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ABBREVIATIONS USED IN TEXT

AV = atrioventricular
ECG = electrocardiographic

Electrocardiographic abnormalities were found in 12 of 25 patients younger than 40 years, with an incidence of 0.64 abnormalities per patient. Of patients older than 40 years, 14 manifested 26 abnormalities, yielding an incidence of 1.3 abnormalities per patient. The incidence of conduction system abnormalities increased significantly with patient age, but even in patients younger than 40 years, 6 of 25 (24%) had a conduction abnormality. Of 20 patients older than 40, 11 (55%) showed conduction abnormalities on their entry ECG. There were no sex differences in the incidence of conduction abnormalities.

Progression of Electrocardiographic Abnormalities

All 45 patients were observed for an average of 55.2 months (range, 12 to 177), or 4.6 years. Of the 45 patients, 36 were followed for at least two years. During the follow-up period, a total of 32 new ECG abnormalities occurred in 21 patients (47%). In eight patients (18%), more than one new abnormality developed. The incidence of any ECG abnormality increased from 58% to 78% during follow-up.

Widening of the QRS complex occurred in 11 patients. New left axis deviation developed in three patients. Abnormal Q waves appeared in three, and the number of patients with increased anterior forces more than doubled, from four to nine. New conduction abnormalities developed in 11 patients. In patients with first-degree AV block at entry, the PR interval was not significantly prolonged during follow-up (PR interval at entry was 0.21 ± 0.02 seconds, mean ± standard error of the mean; PR interval on last follow-up was 0.23 ± 0.03 seconds; *P* not significant), although new first-degree AV block was noted in six patients. In one patient, who had left axis deviation at entry, left anterior hemiblock developed during follow-up. Complete bundle branch block developed in four other patients. The occurrence of nonspecific interventricular conduction delay increased from 16% to 36%. The incidence of bifascicular block increased from 7% to 13% during follow-up. Second-degree or complete heart block did not develop in any patient during the follow-up period.

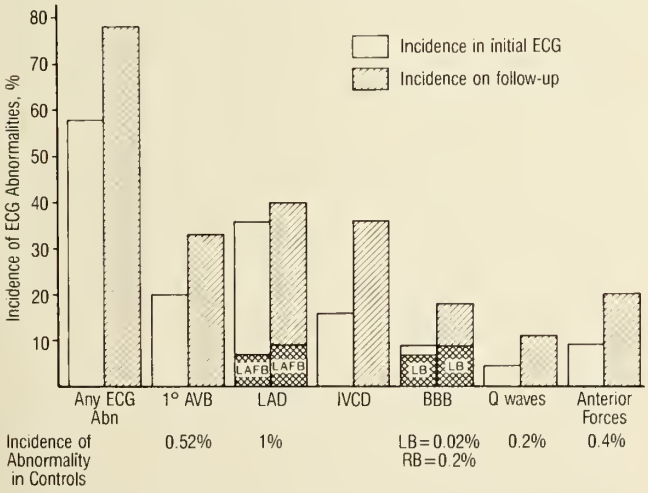

Figure 1.—The chart shows the incidence of electrocardiographic abnormalities at entry and during follow-up in 45 patients with myotonic dystrophy. Shown below the abscissa is the incidence of the electrocardiographic abnormality in 67,375 controls (from Averill and Lamb[14]). Abn=abnormality, 1° AVB=first-degree atrioventricular block, BBB=bundle branch block, ECG=electrocardiogram, IVCD=nonspecific interventricular conduction delay, LAD=left axis deviation, LAFB=left anterior fascicular block, LB=left bundle branch block, Q waves=abnormal Q waves, RB=right bundle branch block

None of the patients had a pacemaker at entry, but five underwent permanent pacemaker placement during the follow-up period. Symptomatic sinus bradycardia (syncope) had developed in one patient, two had asymptomatic sinus bradycardia, one had left anterior fascicular block, and one had first-degree AV block and left bundle branch block. No deaths occurred in the patients not having a pacemaker during the follow-up period. Of those receiving permanent pacemakers, one patient with asymptomatic sinus bradycardia and a family history of sudden death in two affected siblings died suddenly at home. Monitor strips from the emergency department showed pacer spikes at the programmed rate without ventricular capture. The family declined an autopsy. The other four patients who had undergone implantation of a permanent pacemaker remained asymptomatic during follow-up.

Correlation to Disease Severity

Ventricular function was not formally assessed. Only three patients, however, described symptoms of dyspnea, one had edema, and none reported paroxysmal nocturnal dyspnea. On physical examination, none of the 45 patients had signs of right or left ventricular failure. Serial chest x-ray films of 19 patients were available for review and showed normal cardiac silhouette in all but 1 patient, whose cardiac function was normal by radionuclide angiography. Thus none of the patients had evidence of ventricular dysfunction.

No correlation was seen between the presence of ECG abnormalities on entry and the severity of neuromuscular disease as reflected by cranial muscle involvement or muscle impairment. Similarly, there was no relation between the progression of ECG abnormalities and disease severity.

Of the 45 patients, 13 (29%) had experienced palpitations, syncope, or paroxysmal dyspnea on at least one occasion, but the incidence of these symptoms was not significantly different between those with or without ECG abnormalities at entry and those with or without new abnormalities during follow-up. Clinical evaluation, including telemetry and 24-hour Holter examination, failed to show arrhythmias corresponding to these symptoms in any patient. Ambulatory ECG monitoring was done in 12 patients: 4 were normal (except for conduction abnormalities or sinus bradycardia); 3 had asymptomatic, intermittent atrial fibrillation or paroxysmal supraventricular tachycardia (with moderate ventricular response); and 7 (including 2 with supraventricular arrhythmias) had rare to frequent asymptomatic premature ventricular beats. No ventricular tachycardia or ventricular couplets were observed.

Discussion

The prevalence and progression of electrocardiographic abnormalities as reported in this study represent observations in patients with myotonic dystrophy from a neurology clinic cohort unselected for cardiovascular symptoms or abnormalities. Nevertheless, the incidence of ECG abnormalities is higher in patients with myotonic dystrophy than in an otherwise normal control population.[14] Electrocardiographic abnormalities were present in 26 of the patients (58%) on entry in this study. This figure is similar to the 45% to 86% reported in other studies (Table 1).[2-5,7,10] Conduction disturbances—first-degree AV block, interventricular conduction delay, fascicular block, or bundle branch

TABLE 1.—*Incidence of Electrocardiographic Abnormalities in Patients With Myotonic Dystrophy*

Reference Source	*Patients, No.*	*ECG Abnormality, %*	*Left-Axis Deviation, %*	*1°AV Block, %*	*LBBB, %*	*RBBB, %*	*Bifascicular Block, %*	*Complete Heart Block, %*
DeWind and Jones, 1950[2]	98	62	..	..	..	..	..	3
Fisch, 1951[3]	85	68	..	48	..	..	..	0
Payne and Greenfield, 1963[4]	47	45	23	11	4*	4*	..	0
Church, 1967[5]	300	86	19	38	11*	11*	..	0.4
Fearrington et al, 1964[7]	17	70	30	30	..	..	..	0
Moorman et al, 1985[10]	46	72	9	33	0	2	..	0
Present study								
At entry	45	58	36	20	7	2	7	0
During follow-up	45	78	40	33	9	9	13	0

AV=atrioventricular, ECG=electrocardiogram, LBBB=left bundle branch block, RBBB=right bundle branch block

*The patients in these two studies had both right and left bundle branch block.

block—were the most common finding (17 patients, or 38%) and increased with time.

Previous studies on the progression of ECG abnormalities in patients with myotonic dystrophy suggest a slow progression of conduction system disease. Moorman and co-workers[10] retrospectively reviewed previous (4 months to 13 years) ECGs in 30 patients and found a prolongation of the QRS duration in 2 persons and the development of 2:1 AV block in 1. They found no evidence of a progression of ECG abnormalities in the other 27 patients. Prystowsky and associates examined nine patients with serial electrophysiologic studies, a mean of 35 months apart.[11] At the second study, more patients had a prolonged infranodal conduction time. The course of the progression was unpredictable, however, and clinically significant block did not develop in any patient. Örndahl and colleagues reported a slow increase in both PR interval and QRS duration over 1 to 26 years in 23 patients.[15]

This is the first prospective analysis of the progression of ECG abnormalities in a large population of patients with myotonic dystrophy. Electrocardiographic changes developed at a rate of about one new abnormality for every six patients with myotonic dystrophy per year. New conduction disturbances occurred in 11 patients (24%), and the overall prevalence of first-degree AV block, interventricular conduction delay, and fascicular or bundle branch block increased from 38% to 62%. The incidence of bifascicular block nearly doubled, but none of the patients showed complete heart block on entry or during the follow-up period.

The low incidence of high-grade block noted is consistent with that of other prospective studies.[9-11] Higher frequencies of complete heart block have been reported in literature reviews such as that of DeWind and Jones, who reported a 3% incidence.[2] Retrospective literature reviews, however, probably overestimate the actual incidence of the infrequent phenomenon because it is more often reported. Anecdotal reports of complete heart block in patients with myotonic dystrophy[16-20] are difficult to interpret. In at least two of these cases, AV block developed before other features of myotonic dystrophy in patients who were in their 50s.[16,17] The causal relationship of myotonic dystrophy in these cases may be questioned because idiopathic conduction system disease can also be observed in this age group.[21]

Sudden death is reported in 0% to 4% of patients with myotonic dystrophy[10] and is frequently ascribed to the development of complete heart block. In light of the apparently rare occurrence of high-grade AV block, we think other possible causes of sudden death may be more important. This view is supported by several observations. First, we and others have noted that sudden death may occur despite the presence of a pacemaker.[9,22,23] In the case we report, there was no evidence of pacemaker malfunction. Second, other possibly fatal abnormalities can occur in patients with myotonic dystrophy, including sleep apnea and pulmonary hypertension,[24] mitral valve prolapse,[25] left ventricular failure,[5,22,23] and ventricular arrhythmias. In several cases of monitored sudden death or syncope, including those reviewed by Moorman and co-workers,[10] ventricular arrhythmias have been documented as the cause of death. In several case reports, potentially lethal ventricular arrhythmias have been recorded in patients with myotonic dystrophy by ambulatory monitoring[5,17,20,22,23] or by invasive electrophysiologic evaluation.[26] Nevertheless, no prospective study has defined the incidence of either spontaneous or inducible ventricular arrhythmias in these patients. The role of ventricular arrhythmias in patients with myotonic dystrophy remains speculative, but we think it has probably been underestimated.

Electrocardiographic patterns suggestive of coronary artery disease (pathologic Q waves or increased anterior forces) were present in five of our patients (11%), although the mean age of this subgroup was 43 years and no ischemic symptoms were present. New pathologic Q waves and increased anterior forces developed in eight patients (18%), and their overall incidence increased from 11% to 27%. Only two patients had clinical signs of coronary artery disease, and none appeared to have congestive failure. Thus the development of ECG features suggestive of infarction and clinical coronary artery disease may be misleading in this group[7] and should be interpreted with care.

There appears to be no correlation between the degree of disease severity and the presence or progression of ECG abnormalities in patients with myotonic dystrophy. This conclusion, derived from an objective observation of neuromuscular involvement, confirms similar impressions made on the basis of retrospective literature reviews.[5,8,9] Apparently the pathologic process can affect skeletal and cardiac tissue to different degrees.

Electrocardiographic abnormalities in patients with myotonic dystrophy frequently progress even during a relatively short follow-up. Most abnormalities are, however, clinically insignificant conduction disturbances, the development of pseudoinfarction patterns without clinically apparent coronary artery disease, and widening of the QRS complex. Nevertheless, these results should be interpreted with caution because no extensive evaluation of ventricular function was done in our patient population, these patients were relatively young (though typical for a similarly affected patient population), and the follow-up period was short for this chronic neuromuscular disease.

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Articles

An Outbreak of Illness Among Aerospace Workers

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A multispecialty panel of physicians evaluated a case series of 53 composite-materials workers in a large aircraft manufacturing facility who filed workers' compensation claims for illness labeled by the media as the "aerospace syndrome." Possible skin and respiratory tract exposures included formaldehyde, phenol, particulates, epoxy resins, and trace organic solvents, but measured concentrations were well below all regulatory and consensus standards. Most workers had histories of transient skin or respiratory tract irritation consistent with the known potential toxicity of these materials. None of the workers tested had immunoglobulin IgG or IgE antibodies to human serum albumin complexed with formaldehyde. A majority (74%) met DSM-III-R [*Diagnostic and Statistical Manual of Mental Disorders,* 3rd edition, revised] criteria for major depression, panic disorder, or both. Most of these psychiatric disorders were of a recent onset, correlating in time with the use of phenol- and formaldehyde-impregnated composite material. Psychosocial factors were thought to have played a major role in the high prevalence of illness in this group and should be evaluated directly in well-controlled epidemiologic studies of similar crisis-building situations in the future.

(Sparks PJ, Simon GE, Katon WJ, et al: An outbreak of illness among aerospace workers. West J Med 1990 Jul; 153:28-33)

By mid-1988, more than half of approximately 200 employees working with composite plastic materials in one building of a large aircraft manufacturing company reported multiple symptoms including dizziness, nausea, headaches, fatigue, shortness of breath, palpitations, and cognitive impairment. The composite materials were composed of fiberglass, graphite, and other synthetic fibers. These fibers were impregnated with epoxies or phenol-formaldehyde resins and cured with heat to form rigid aircraft parts. For most workers, the symptoms were reported to begin within one week to six months after the introduction of fiberglass cloth impregnated with phenol-formaldehyde resin (phenolic material) in mid-1987 to comply with Federal Aviation Administration regulations regarding fire retardation.

Most of the workers reporting symptoms had been referred by their fellow workers and the local union to an allergist in the community. Some workers had been referred by the allergist to a psychiatrist who diagnosed permanent organic brain damage said to be "typical" of toxic chemical exposure. The allergist announced to the media the presence of a new disease, the "aerospace syndrome." Workers understood from these physicians that they had antibodies to formaldehyde, immune system dysfunction, and brain damage. This prompted several months of local and national media coverage, intense union-management deliberations, and a United States Senate subcommittee hearing on the issue.

After industrial hygiene evaluation, the cause of the new "aerospace syndrome" remained unclear. Despite industrial hygiene data showing workplace chemical exposures well below those typically considered risks to health, an increasing number of workers became ill and disabled. The manufacturer and the workers' compensation administrator enlisted one of us (P.J.S.) to conduct an independent medical evaluation of all of the workers filing compensation claims. A multidisciplinary panel was convened and included specialists in occupational medicine-clinical toxicology, allergy-immunology, and psychiatry with consultants in neurology, dermatology, and pulmonary medicine. The following is a case-series presentation of the clinical findings.

Patients and Methods

Industrial Process and Exposure Monitoring

Those involved in the outbreak worked primarily with fiberglass impregnated with phenol-formaldehyde resin, although epoxy resins had also been used in the same area for several years. The process, called "lay-up," involved hand molding and oven curing of the composite material. Some parts required reworking with saws and routers and filling in defects with epoxy or phenolic compounds. Small amounts of organic solvents were used for cleaning the parts and molds. Suspected chemicals included phenol, formaldehyde, epoxy resins, and trace amounts of styrene, antimony trioxide, methylene chloride, acetone, C9 through C12 alkanes, C9 through C12 aromatics, salicylaldehyde, and methanol. Disposable plastic laboratory coats, sleeves, and gloves were available (but optional) until the spring of 1988 when the use of gloves became mandatory. Half-mask respirators with organic vapor-acid gas cartridges were also made available at that time.

During 1987 and again in the spring of 1988, extensive personal air monitoring for phenol, formaldehyde, total particulates, and antimony trioxide was obtained by the company using industrial hygiene methods published by the National Institute of Occupational Safety and Health (NIOSH).[1] During the summer of 1988, similar air monitoring, which also included styrene, acetone, and methylene chloride, was carried out by the Washington State Division of Occupational Safety and Health and NIOSH using the same methods. Thermatogravimetric and gas chromato-

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
DIS = Diagnostic Interview Schedule
ELISA = enzyme-linked immunosorbent assay
GC-MS = gas chromatographic-mass spectrophotometric
HSA = human serum albumin
NIOSH = National Institute of Occupational Safety and Health

graphic-mass spectrophotometric (GC-MS) analysis[2] of the phenolic material was also done by the University of Washington Department of Environmental Health, the aerospace company, and NIOSH.

Worker Selection

In all, 60 workers filed compensation claims during 1988 for health complaints possibly related to work with the phenolic material. Seven workers failed to report for examination. Of the no-shows, six said that their symptoms, involving multiple organ systems, had completely resolved. Evaluations of a total of 53 workers with exposure to phenol-formaldehyde composite materials are included in this report.

Clinical Evaluation

Each worker was initially seen by an occupational medicine specialist-internist. A detailed occupational and medical history was obtained, and a physical examination, including a neurologic examination, was done. Most of the workers were also evaluated by an allergist-immunologist. Current and past medical records, before occupational exposure, were reviewed. Blood specimens were drawn for liver, kidney, and thyroid function studies, electrolytes, and complete blood count with differential. A urinalysis and screening spirometry were obtained.

Immunologic Evaluation

Serologic assays for formaldehyde complexed with human serum albumin (HSA-formaldehyde) were analyzed at Northwestern University Division of Allergy/Immunology by enzyme-linked immunosorbent assay (ELISA) according to previously published methods.[3] This test, done on specimens from the first 33 workers filing compensation claims, measures titers of immunoglobulin IgG and IgE antibodies to HSA-formaldehyde and HSA alone in the serum of the subjects. The test was standardized using serum from three known negative controls and a positive control. The specimens were analyzed by two senior technicians using coded specimens without knowledge of clinical information. Any serum producing an optical density greater than twice that of the control serum was retested twice by each technician.[4]

Neuropsychiatric Evaluation

Each subject completed several self-report questionnaires. These included the SCL-90-R,[5] the Whiteley Index,[6] and a questionnaire devised by one of us (G.E.S.) to assess symptoms on exposure to a variety of chemicals. The SCL-90-R is a 90-item checklist assessing the presence of somatic and psychological symptoms on a 0 to 4 severity index. Raw scores were converted to standardized (T-score) norms for nonpatient populations.[5] The Whiteley Index (a version of Pilowsky's Illness Behavior Questionnaire) is a 14-item self-report scale assessing hypochondriacal beliefs and behavior. It has been found to discriminate between hypochondriacal patients and medical controls. Last, the patients completed a questionnaire assessing the presence of symptoms of "multiple chemical sensitivity." This was defined as the reporting of multiple somatic symptoms on exposure to low levels of a variety of chemically unrelated substances (such as automobile exhaust, perfumes, new carpet odor, and newsprint), in both the occupational and nonoccupational settings, that were not associated with objective findings of organ system impairment or physiologic dysfunction.[7]

All subjects also underwent a structured psychiatric evaluation using the National Institute of Mental Health's Diagnostic Interview Schedule (DIS).[8] The DIS is a highly structured interview that investigates the presence of symptoms of major psychiatric illnesses and assigns current (within the past six months) and past diagnoses according to criteria[8,9] of the *Diagnostic and Statistical Manual of Mental Disorders*, third edition, revised. The DIS was used instead of a free-flowing psychiatric interview to allow a more objective and standardized evaluation of the presence of psychiatric illness. The interview protocol systematically evaluates each reported symptom to determine its relation to medical illness, drug or alcohol use, or psychiatric illness. One section of the interview specifically assesses how often respondents have sought care for medically unexplained physical symptoms. The DIS interview includes Folstein's Mini-Mental State examination,[10] a brief test of cognitive ability. This instrument has excellent reliability and validity and has been found to correlate well with more extensive neuropsychological testing.[11] Five patients were interviewed by two psychiatrists to ensure uniformity of use of the DIS. Past psychiatric diagnoses were determined by the reporting of past psychiatric symptoms on the DIS and a review of past medical records.

After these examinations, workers with dermatologic signs were evaluated by a dermatologist. Those with Mini-Mental State examination scores of 25 or less or with complaints of cognitive dysfunction were subsequently referred for evaluation with a standard battery of neuropsychological tests.[11] These included measures of attention and concentration, executive control and problem solving, language, visuospatial orientation, memory, sensory perception, motor function, cognition, emotion, personality, and motivation. Because depression and anxiety may cause mild abnormalities of cognitive function on neuropsychological testing,[11] all subjects underwent a psychiatric evaluation before such testing. Workers with a subjective sensory loss were evaluated by a neurologist and underwent nuclear magnetic imaging of the head, nerve conduction studies, or both. Those with symptoms of airway reactivity and normal spirometric values underwent methacholine challenge testing.

Results

Air Monitoring Data

Thermatogravimetric GC-MS analysis of the phenolic material failed to reveal the presence of significant quantities of unsuspected materials. Airborne levels of phenol, formaldehyde, antimony trioxide, total particulates, styrene, and other trace organic compounds measured by the company, the state, and NIOSH were well below federal permissible exposure limits (Table 1). Those filing compensation claims did not have significantly different exposures from those in the same work area who did not.

Clinical Information

Of the 53 workers, 44 (83%) were women and 27 (51%) were currently cigarette smokers. Smoking did not affect the number of reported symptoms. There was no difference in the range of symptoms reported by the 49 workers who

consulted the local allergist compared with the 4 workers who did not. Symptoms did not vary significantly by job category, duration of exposures, or location within the composite production area. The exposure concentrations were so uniformly low, it was not possible to distribute workers into meaningful exposure groups so that a dose-response relationship of symptoms and exposures could be assessed.

The summary of the clinical findings appears in Tables 2 and 3. Sensory or upper respiratory tract irritation (or both) was seen in 39 (74%) workers. Sensory irritation was defined as headache or nausea associated with the odor of the phenolic material. Nineteen (36%) also reported dermatitis. A history of skin rash was associated with an initial lack of glove use. Most of the workers with dermatitis also had symptoms of upper respiratory tract or sensory irritation.

Fifteen workers (28%) described symptoms consistent with the "multiple chemical sensitivity syndrome."[7] Four of the workers (8%) described sensory loss in the extremities that was not confirmed by objective neurologic signs or diagnostic testing.

In general, the physical examinations of these workers revealed few objective findings. Five of seven workers with findings of upper respiratory tract irritation had histories of atopic disease. Eight workers had evidence on spirometry, or methacholine challenge, of reactive airways disease. In five of these workers, this was explained by either previously symptomatic atopy or asthma. Results of the other laboratory tests (complete blood count, liver and kidney functions, electrolytes) were generally unremarkable.

Immunologic Evaluation

The first 33 subjects had analyses of serum by ELISA to measure serum levels of IgE and IgG antibodies to HSA-formaldehyde. There were no differences between workers' results and controls. For this reason and because of the high cost of this assay, the test was not done on the rest of the group.

Neuropsychiatric Evaluation

The most striking finding of the psychiatric evaluations was the high prevalence of anxiety and depressive disorders (Table 4). Only 14 subjects had no diagnosis of depression or panic disorder associated with their current symptoms. The high prevalence of current psychiatric diagnoses correlated in time with work with phenol-formaldehyde composites and was not well explained by preexisting psychiatric disease (Table 4). Scores on the SCL-90-R also showed a high level of current psychiatric symptoms. Most subjects had scores in all subscales except paranoia that were greater than two standard deviations above the mean for the general population. All scales showed similar degrees of elevation. For most, current psychiatric symptoms had not lessened substantially with removal from work with phenol-formaldehyde composites at the time of this evaluation.

A subset of subjects, most with past symptoms of psychiatric disorders, appeared to have a preexisting tendency toward somatization (Table 4). Three qualified for the diagnosis of somatization disorder[9] by the DIS interview and a review of medical records. Using an abridged definition of somatization proposed by Escobar and co-workers (four medically unexplained symptoms for a man and six for a woman),[12] 14 subjects had a previous tendency to present with medically unexplained physical symptoms thought to be based on psychological distress and had Whiteley Index scores typical of hypochondriacal persons. Most of these were the same subjects who met our definition of having the "multiple chemical sensitivity syndrome,"[7] whose characteristics are described further in another publication.[13] In the abridged definition, somatization (somatization trait) has been shown to be associated with an increased and preferential use of medical versus mental health services when psychiatric illness is present. For the entire group, the mean score on the Whiteley Index was 5.0, lying between

TABLE 1.—*Summary of the Air Monitoring Data in 53 Aerospace Workers With Workplace Exposures*

Substance	*Measured Values*	*Permissible Exposure Limits**
Phenol, ppm	0.001-0.180	5
Formaldehyde, ppm	0.003-0.073	1
Antimony trioxide, mg/m³	BDL	0.5
Total particulates, mg/m³	0.48-1.1	10
Styrene, ppm	BDL-1.2	100
Methylene chloride, ppm	BDL-0.1	100
Acetone, ppm	BDL-7.6	1,000

BDL=below detection level for method used, ppm=parts per million

*Federal Occupational Health and Safety Administration Standards.

TABLE 2.—*Summary of Subjective Complaints in 53 Aerospace Workers With Workplace Chemical Exposures*

Symptom	*Subjects, Number*	*%*
History of contact dermatitis	19	36
Episode of hives	3	6
Sensory irritation	39	74
Eye and upper respiratory tract irritation	30	57
Lower respiratory tract irritation	19	36
Gastrointestinal symptoms	8	15
"Multiple chemical sensitivity"	17	32
Numbness of extremities	4	8
Multiple somatic complaints	16	30
Difficulty with memory and concentration	22	42

TABLE 3.—*Summary of Objective Findings in 53 Aerospace Workers With Workplace Chemical Exposures*

Sign	*Subjects, Number*	*%*
Contact dermatitis	2	4
Upper respiratory tract inflammation	7	13
Airway reactivity on spirometry or methacholine challenge	8	15
Elevated serum thyroxin	4	8
Hematuria	3	6

TABLE 4.—*Summary of Neuropsychiatric Findings in 53 Aerospace Workers With Workplace Chemical Exposures*

Finding	*Subjects, Number*	*%*
Current depression	32	60
Past depression	12	23
Current panic disorder	14	26
Current panic attacks	3	6
Past panic disorder	2	4
Somatization disorder	3	6
Somatization trait	14	26
Abnormal findings on Mini-Mental State* examination	4	8

*The Mini-Mental State examination is part of the National Institute of Mental Health's Diagnostic Interview Schedule (Robins et al8).

scores typical of hypochondriacal patients and normal nonpatient controls.[6]

Four of the workers had abnormal findings on the Mini-Mental State examinations. For most, the deficit consisted of the inability to subtract 7's from 100. Subsequently, 25 of the workers with abnormal Mini-Mental State examinations, neuropsychological symptoms (such as reduced memory and difficulty with concentration), or both, were referred for detailed neuropsychological testing. None were reported to have significant cognitive deficits of recent onset or correlated with exposure to phenol-formaldehyde composites.

Discussion

More than half of subjects had histories of local symptoms consistent with contact dermatitis, mucous membrane irritation, or both. A few showed physical signs of such irritation at the time of this evaluation. These symptoms and signs were consistent with the known toxicities of the potential chemical exposures present at the work site.[14-19] Most of these local irritant symptoms resolved rapidly without long-term sequelae following removal from exposure.

In contrast, many of the workers had chronic and systemic health complaints that were not consistent with the known toxicity of the materials to which they likely had exposure. For example, it is known that skin exposure to formaldehyde can produce both irritant and allergic contact dermatitis and probably urticaria.[14] Formaldehyde has also been causally related to upper and lower respiratory tract irritation, and rare cases of asthma have been documented in persons with ongoing exposure.[14-16] There are, however, no adequately controlled studies to support the contention that subacute or chronic formaldehyde exposure can produce systemic symptoms such as fatigue, a loss of memory, difficulty in concentrating, or depression.[14-19] There is no evidence that low-level formaldehyde exposure causes organic brain dysfunction or abnormal neuropsychological test results.[14-20] The rapid metabolism of formaldehyde makes systemic effects unlikely.[21] Moreover, smokers have exposure to relatively high levels of formaldehyde,[22] but cognitive dysfunction has not been reported as more prevalent in this group.

Other chemicals to which these workers could have been exposed, such as phenol, styrene, acetone, or antimony trioxide, may be associated with systemic symptoms that follow a dose-response relationship.[19] Symptoms associated with acute exposure, such as headache, respiratory tract irritation, or nausea, are usually temporary and abate with removal from exposure. Very high exposure over several years may be associated with irreversible impairment of the nervous system, liver, or kidneys, which can be documented with objective tests.[19,23] Such effects have been observed with much higher concentrations and longer durations of exposure than has occurred in this setting.

The potential exposures in this workplace do not include exotic chemicals with which occupational medicine has little experience. Low-level exposure to these substances, individually and as chemical mixtures, occurs every day in hundreds of industries without incident.

The diagnosis of "mass hysteria" is made with specific criteria—which include a rapid onset, verbal or visual transmission of illness, and a predominance of symptoms of hyperventilation—that do not entirely explain the timing or the range of symptoms and signs in this group of workers.[24] On the other hand, this outbreak of illness has much in common with "crisis building" situations described by Baker[24] in which the onset of illness is slower with a wider range of symptoms reported.

A thorough medical evaluation failed to reveal objective abnormalities that might explain these workers' disabling symptoms. The immunologic evaluation was similarly unrevealing. Most of the subjects reported previous unusual immunologic tests, ordered by a local allergist who had cared for many of the workers affected by this outbreak and carried out by a commercial laboratory. Results of these tests indicated low titers (1:4 to 1:32) of IgG or IgM antibodies to formaldehyde, trimellitic anhydride, or isocyanates complexed with HSA, as well as "elevations" in the number or proportion of TA-1 receptor-positive lymphocytes. Various "positive" autoantibodies were also reported to have been found. Most workers believed that such results indicated that their exposures to "chemicals" were "high" and that their symptoms resulted from "chemical poisoning" or "allergy to chemicals." Some described concern about "chemical AIDS [acquired immunodeficiency syndrome]."

A careful review of the literature raises many questions about the pathophysiologic significance of this battery of immunologic studies. The reported presence of antibodies to HSA-formaldehyde was not replicated by this study's controlled evaluation, which suggests that either the antibodies had disappeared (some workers had been removed from work with phenol-formaldehyde composites), antibodies were never present at all, or there were significant differences in methodology between the commercial and university laboratories. Patterson and associates have said that there is insufficient evidence to support a relationship between gaseous exposure to formaldehyde and the presence of antibodies to HSA-formaldehyde and systemic hypersensitivity or illness.[25] In addition, low titers of autoantibodies frequently may be found in healthy persons.[26]

The use of such an extensive battery of laboratory tests to support an immunologic basis for illness in these workers is unsubstantiated.[27] For many of the tests used, there are little data to indicate what a normal result should be for healthy persons. A wide variation in the types of "abnormal findings" among subjects with similar clinical syndromes suggests that such findings may represent chance occurrence. Immunologic data can only be accepted as useful in the diagnosis of illness related to chemical exposure when well-designed epidemiologic studies reveal consistent correlations of such measures with specific exposures and disease states. Existing reports use inadequate controls and fail to consider important factors of case selection, smoking, other chemical exposures, and the presence of other illness such as atopy.[28-30] Finally, these test batteries are costly.

The most striking finding from this group evaluation was the 74% prevalence of major depression, panic disorder, or both, in these workers. A majority of workers had psychiatric illness develop that was correlated in time with exposure to the phenolic material and a confluence of psychosocial factors. If only symptoms predating work with the phenolic material were considered, the prevalence rates of preexisting psychiatric diseases were 4% for panic disorder and 23% for major depression. These prevalence figures are considerably higher than those found in the general population (3% to 4% for depression),[31] but they are similar to rates reported for patients visiting general medical clinics.[32-34] Thus, this group of workers displayed a high prevalence of anxiety and depression not explained by preexisting psychiatric illness.

Psychiatric diagnoses in this group probably explain many of the somatic symptoms such as fatigue, difficulty

with concentration and memory, sleep disturbances, dizziness, and palpitations. Patients with major depression and panic disorder have been found to use more nonpsychiatric medical care[35-37] and to complain of more symptoms[37-39] than do nondepressed controls. The tendency for affective illness to lead to increased somatic symptoms, a poorer perception of one's health, and an increased perception of disability and impairment in a person's vocational and social roles has been described previously.[40] Symptoms of depression or panic in many of these workers may have been exacerbated by the mistaken impression that they suffered from "brain damage" or were "poisoned," their immune system was damaged, or that they had "chemical AIDS" because of their occupational exposure to "chemicals."

The high incidence of new cases of panic disorder suggests that there may be significant interaction between the sensory and irritant stimulation of the mucous membranes of the upper respiratory tract and the autonomic or central nervous system reaction to such stimulation. Numerous subjects described episodes of dizziness, palpitations, dyspnea, and faintness occurring at times of exposure to volatile materials associated with a pungent odor. In many subjects experiencing such attacks, clinical syndromes then developed that were indistiguishable from typical panic disorder.

Previous case reports describe the precipitation of panic disorder by exposure to solvents or other respiratory irritants with a noxious odor.[41,42] Such reactions are difficult to explain by a direct toxic effect of the specific chemicals on the central nervous system. Some of the substances precipitating these reactions, such as chlorine or formaldehyde,[19,21] are not systemically absorbed. Instead, irritant symptoms coupled with a fear of toxicity may produce a state of autonomic arousal leading to a panic attack. Such a chain of events can be postulated to lead to a conditioned response in which subsequent exposures could produce similar panic attacks with their associated physical symptoms.[43] This mechanism has been described by Shusterman and colleagues as "behavioral sensitization to odorants."[44]

Our findings suggest that psychiatric morbidity may explain much of the illness and disability experienced by this group of workers. There is accumulating evidence that long-term exposure to mixed organic solvents can cause organic brain syndromes with anxiety and depressive symptoms as prominent components.[23,45-49] In these studies, however, workers with solvent neurotoxicity had exposure to far higher levels of solvents for much longer durations than the subjects of this report. Although we cannot absolutely exclude that this outbreak of symptoms of anxiety and depression could have resulted from unknown neurotoxic effects of very low levels of mixed chemical exposures, this possibility seems unlikely.

This study is most limited by the fact that all patients were seen during a workers' compensation evaluation process and that this circumstance precluded the evaluation of a control group. Symptom reporting in a subset of this group of workers with exposure to phenol-formaldehyde composite materials was compared with that of a similar group of workers in another facility within the same company not working with this material.[50] This comparison showed that the employees working with phenol-formaldehyde had a higher proportion of female workers, had worked for the company a shorter time, and had a higher prevalence of self-reported respiratory tract symptoms and hand rashes than the reference group. The prevalence of psychiatric symptoms was not addressed, however.

Some workers clearly considered psychiatric evaluation as an attempt to prove the psychological origin of their symptoms and thus deny them compensation. Such a bias would likely have resulted in a falsely lowered prevalence of psychiatric illness and psychological morbidity. In contrast, the finding of high levels of psychiatric morbidity in this population might have resulted from ill workers with psychological symptoms being more likely to seek workers' compensation. If such selection occurred, psychiatric illness would be overrepresented among this group as compared with other workers affected by this same outbreak who did not file claims. Even if none of the other affected workers had psychiatric illness, however, the prevalence of such illness is higher than expected.[31]

Psychosocial factors in the workplace and the community are likely to have been major contributors to this outbreak of illness. A recent study of a similar outbreak reported that work intensity and mental strain were the most important variables predicting severity of illness.[51] Many of our subjects described such factors as increased production pressure, tense labor-management relations, worker perception of inadequate management attention to safety, and reinforcement of fear by co-workers, the media, and medical providers. Many workers were alarmed by the perception that their immune system was damaged and that they were poisoned or seriously ill. Psychosocial factors should be evaluated directly in well-controlled epidemiologic studies of similar crisis-building situations in the future.

Whether these psychiatric symptoms were caused by sensory or respiratory tract irritation from low-level chemical exposure, or primarily psychosocial factors and the effects of the fear of chemicals, they have clearly caused much distress and functional disability. There are specific and effective treatments that can relieve the psychiatric and physical distress generated by these illnesses.[34,35,37] Unfortunately, the label "aerospace syndrome," and the avoidance of all chemical exposures and the workplace recommended by some health care practitioners, may only perpetuate illness and reinforce disability.[52]

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Articles

Cancer Risks and Prevention Practices Among Vietnamese Refugees

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Although Vietnamese refugees are the fastest-growing Asian minority in the United States, little is known about their health knowledge and practices, especially regarding cancer prevention. To address this problem, we interviewed a randomly selected sample of 215 Vietnamese adults living in the San Francisco Bay Area. Results indicated that 13% had never heard of cancer, 27% did not know that cigarette smoking can cause cancer, and 28% believed that cancer is contagious. Although hepatitis B-related liver cancer is endemic among Vietnamese, 48% had never heard of hepatitis B. Among men (n = 116), 56% were smokers (versus 32% in the general US population). Male cigarette smoking was significantly associated with incomes below the poverty level ($P < .01$), residence in the US for 9 years or less ($P < .05$), not knowing that smoking causes cancer ($P < .05$), and limited English proficiency ($P < .01$). Binge drinking was reported by 35% of men. Young Vietnamese of both sexes reported consuming diets higher in fat and lower in fiber than when they lived in Vietnam. Among eligible women, 32% had never had a Papanicolaou test (versus 9% of US women), 28% had never had a breast examination (versus 16%), and 83% had never had a mammogram (versus 62%). Education about cancer and its risk factors, smoking cessation, and cancer screening are high priorities for this population.

(Jenkins CNH, McPhee SJ, Bird JA, et al: Cancer risks and prevention practices among Vietnamese refugees. West J Med 1990 Jul; 153:34-39)

In the 15 years since 1975, the number of Vietnamese living in the United States has climbed to 725,000 (Linda Gordon, PhD, Office of Refugee Resettlement, US Department of Health and Human Services, oral communication, April 1989).[1] Vietnamese are the fastest-growing Asian-Pacific minority in the United States.[1] Population projections indicate that by 2030 they will vie with Filipinos in being the largest Asian-Pacific minority in the country.[1]

Preliminary data have suggested possible excess cancer mortality at certain sites among Vietnamese.[2] Certain behaviors, including cigarette smoking, excessive dietary intake of fat,[3] low dietary intake of fiber,[3] and consumption of alcohol,[4] have been linked epidemiologically to an increased risk of cancer. In the Vietnamese population in particular, the high seroprevalence of hepatitis B surface antigen (HBsAg)* poses a risk for liver cancer.[5]

Cancer mortality can be lowered by reducing behavioral risk factors, screening for the early detection of cancer, and providing immunoprophylaxis for the offspring of women who are positive for HBsAg.[6-10] For the Vietnamese immigrant population, however, there are no data on the prevalence of behavioral risk factors, the use of cancer screening procedures, or knowledge of cancer. National surveys do not report data for Vietnamese.[11-13] To obtain these data, therefore, we did a survey of persons in Vietnamese households in the San Francisco Bay Area.

*The prevalence of HBsAg among Vietnamese refugees who arrived in this country from 1984 to mid-1987 was 14.4% (Gregory Pierce, PhD, Centers for Disease Control, written communication, June 1987).

Subjects and Methods

Households for inclusion in the sampling frame were chosen from Vietnamese names listed in the San Francisco and Oakland, California, telephone books. Vietnamese telephone listings, which accounted for 42% of the sampling frame, are easily found because 12 Vietnamese family names account for 85% of all Vietnamese.[14] To gain access to those not listed in telephone directories, we obtained names from the rosters of refugee resettlement organizations, Vietnamese religious organizations, mutual assistance associations, and refugee medical clinics. These sources accounted for the remaining 58% of the sample.

Questions were asked about demographics, health care access and use, knowledge about cancer, health beliefs and practices, the use of cancer screening tests, the prevalence of cigarette smoking, the prevalence of alcohol consumption, and diet. To facilitate comparisons between data for Vietnamese and national data, questions regarding cigarette smoking and alcohol consumption were adapted from the National Health Interview Survey (US Department of Health and Human Services, Office of Smoking and Health, unpublished data, 1987) and the Behavioral Risk Factor Surveillance System Data Collection Instrument (Centers for Disease Control, unpublished data, 1987). Because many respondents were not familiar with several cancer screening tests and their terminology, interviewers explained these procedures before ascertaining respondents' screening status. Interviewers clarified the concept of the stool occult blood test, for example, by showing respon-

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These results were presented in part at the annual meeting of the American Public Health Association, Boston, November, 1988.

This work was supported by the California Division of the American Cancer Society, Contract No. D99-710-12-87.

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dents a sample of the test kit itself. To assess whether dietary changes might be increasing cancer risks in the survey population, interviewers asked respondents if they ate more, the same, or less of four indicator high-fat foods (beef, pork, eggs, and cheese) and two high-fiber foods (green vegetables and fruit) since arriving in the US. Questions about the use of traditional medical practices were open-ended.

The questionnaire was written in English, translated into Vietnamese, and backtranslated into English following the method suggested by Eyton and Neuwirth.[15] We compared the backtranslation with the English original to ensure the lexical equivalence of the Vietnamese version. The questionnaire was pilot tested with members of the target population for comprehension and cultural sensitivity and then revised.

A 14-member community advisory board, made up of leaders in the Vietnamese community, assisted the project staff in the development of the sampling frame and in the writing of the survey questionnaire.*

Using a computer program, a random sample of persons was drawn, and letters in Vietnamese explaining the study were sent to those persons in each household. A few days later, one of two Vietnamese interviewers telephoned the households to make an appointment for an interview. Those for whom no telephone listing could be found were contacted at their residences.

Criteria for inclusion in the sample were Vietnamese ethnicity (defined by self-identification), residence in the San Francisco Bay Area, and age 21 years or older. Some Chinese-Vietnamese (Vietnamese of Chinese ethnic origin) were unintentionally included in the sampling frame because a number of Chinese-Vietnamese have names that are indistinguishable from Vietnamese names. Those who identified themselves as Chinese-Vietnamese were excluded from the sample because earlier research has shown that the two groups differ considerably on a number of demographic variables.[16]

Because key Vietnamese community informants cautioned during survey planning stages that enumerating household members would arouse the suspicion of the interviewers and, thus, lower the response rate, no enumeration was attempted. Therefore, an interview was conducted with the first household member who agreed to it. Face-to-face interviews were conducted in the Vietnamese language and lasted about an hour.

Data were analyzed using standard techniques. Tests of significance included χ^2 for cross-tabulations and F tests for analysis of variance.

Results

The sampling frame consisted of 3,220 persons, and 779 persons—nearly a quarter of the population—were selected for the sample. Of these, 174 did not meet eligibility criteria and 216 had moved, leaving 389 eligible for inclusion in the survey. We interviewed 215 of these, for a response rate of 55%. Interviewers were unable to contact 15 persons, and 159 refused to be interviewed. Of those interviewed, 13% had no known telephone and were, therefore, contacted directly at home.

*The following served as a community advisory board: Arthur Chen, MD; Luu Van Lai; Sister Rosaline Lieu Nguyen, MS; Nguyen Thoa; Vu Duc Vuong; Truong Thi Bach, MD; Nguyen Ngoc Canh, PhD; Chung Hoang Cuong, PhD; Eric Crystal, PhD; Nguyen Van Dinh, MSW; John Driscoll, PhD; Chiang-Peng Ngin, MPH; Nguyen T. Nguyen; and Sally Shankland. These members also assisted in gaining access to respondents, as did Hoang Tuan Anh, MD; Paul Delay, MD; Reverend Thich Quang Chon; Janice Louie, RD; Hai Ninh; John Driscoll, PhD; and Pham Tanh, MD. Thai Vinh Khiem assisted with data collection.

Sociodemographic Characteristics

Based on the survey data, Vietnamese in the catchment area were entirely foreign born (Table 1). Most earned a low income and had not completed a high school education. Nearly half reported no or limited verbal proficiency in English. Most of the respondents reported that they had some form of health insurance. Overall, respondents made a mean of 7.2 physician visits during the past year, but 12% did not see a physician at all.

The San Francisco Bay Area has several private-practice Vietnamese physicians and clinics that provide Vietnamese translators. Most respondents with a regular physician chose to go to one who was Vietnamese. Of those who saw a non-Vietnamese physician, 53% reported that a Vietnamese translator was available during their visits. Only 9% of the total sample reported that they never had a translator when they sought medical care. The use of Vietnamese physicians was not related significantly to respondents' English-language proficiency.

Knowledge

Although most had heard of cancer, there were gaps in the respondents' knowledge about the role of cigarette smoking or diet in "causing" cancer (Table 2). Nearly a third thought that cancer is contagious. A large majority of women (89%) had never heard of the Pap test. By comparison, only 3% of women in the general US population have never heard of this procedure.[17]

The awareness of hepatitis B was low. Having heard of hepatitis B was not associated with sex, age, level of educa-

TABLE 1.—*Sociodemographic Characteristics of Survey Respondents (n=215)*

	Respondents
Sex, %	
Male	54
Female	46
Median age (range), yr	35 (21-78)
Country of birth, % Vietnam	100
Background,%	
Urban	89
Rural	11
Mean number of years in US (SD)	7.6 (3.4)
Spoken-English proficiency, %	
None	24
Limited	22
Fair	26
Good	28
Completed high school, %	41
Employed, %	37
Median household income, $	11,500
Below poverty level, %	53
Health status, %	
Excellent/good	46
Fair/poor	54
Health insurance, %	
None	15
Medi-Cal/Medicare	55
Private	30
Has regular source of medical care, %	89
Ethnicity of regular physician, %	
Vietnamese	47
Non-Vietnamese	17
No regular physician	36
Had ≥1 physician visit last year, %	88

SD=standard deviation

tion, having an income below the poverty level, or number of years of residence in the United States.

Use of Traditional Medical Practices

Vietnamese employ several traditional medical practices.[18-21] To ascertain if the use of traditional medicine interferes with seeking Western treatment of cancer symptoms, interviewers asked respondents what treatment they would choose first for six different symptoms. For symptoms such as headache, cold, or fever, 18% to 43% chose traditional practices (Table 3). But for possible cancer symptoms, such as blood in the stool, a breast lump, or unusual vaginal bleeding or discharge, fewer (1% to 9%) chose traditional treatments. More respondents chose Western treatment.

Smoking

Vietnamese men reported cigarette smoking at a rate almost twice that of US men (56% versus 32%) (Table 4).[22] Vietnamese women, on the other hand, smoke at a third the rate of US women (9% versus 27%).[22] Among Vietnamese men, 16% formerly smoked and 28% had never smoked. Former smokers had quit a mean of 4.5 years ago, and all but one of these had quit after arriving in the US. Among Vietnamese women, none were former smokers.

The mean number of cigarettes smoked per day by male smokers was 13.4 (standard deviation 8.7), lower than the mean number of 23 for US white men[23] but comparable to those of other US minorities. US black men are reported to smoke a mean of 15 cigarettes per day[23] and California Hispanic men a mean of 11 per day.[24] Of the Vietnamese male smokers, 88% reported smoking high-tar, high-nicotine cigarette brands, and 54% reported "always smoking right after awaking in the morning." While most (82%) said they wanted to quit smoking, a majority (71%) thought it would be hard to do so. More than two thirds (69%) reported that their physicians had advised them to quit or reduce smoking.

Vietnamese men who were significantly more likely to smoke were those with incomes below the poverty level ($P < .01$), those who had come to this country within the past nine years ($P < .05$), those who did not know that smoking causes cancer ($P < .05$), and those with limited English proficiency ($P < .01$). There were no significant associations between smoking and education level, consumption of alcohol during the previous month, marital status, employment status, self-reported health status, and age.

Alcohol Consumption and Diet

The prevalence of alcohol consumption was 67% among male respondents but only 18% among female respondents, compared with 66% for men and 47% for women in the general US population (Table 4).[3] The prevalence of heavier drinking among Vietnamese respondents paralleled closely the US rates.

None of the female respondents, but 35% of the male respondents, reported binge drinking. Younger Vietnamese men (ages 21 to 34, n = 46) reported binge drinking less frequently than their counterparts in the general California population (22% versus 35%),[25] but older Vietnamese men (older than 54, n = 15) reported more binge drinking than their California counterparts (20% versus 10%). For men aged 35 to 54 (n = 55), binge drinking rates were comparable among Vietnamese and Californians (25% versus 24%).

As shown in Table 5, although 48% to 73% of respondents reported eating more high-fat foods since arriving in the US, only 13% to 15% reported eating less high-fiber

TABLE 2.—*Health Knowledge of Survey Respondents (n=215)*

Question	Response, % Yes	No	DK/NA
Have you ever heard of cancer?	87	13	..
Does smoking cause cancer?	74	4	22
Do some foods cause cancer?	45	13	42
Do some chemicals in food cause cancer?	59	6	35
Will living near someone with cancer cause cancer?	28	35	36*
Have you ever heard of the Pap test?†	15	85	..
Have you ever heard of hepatitis B?	52	48	..
Have you had hepatitis B?	4	94	2
Do you know someone with hepatitis B?	18	80	2
Do you know anyone vaccinated for hepatitis B?	6	94	..

DK = don't know, NA=not applicable

*Because of rounding of numbers, percentages add up to less than 100%.
†Women only (n=99).

TABLE 3.—*Choosing Traditional Versus Western Treatment for Selected Symptoms (n=215)*

Symptom	Respondents' Treatment Choice, %* Traditional	Western
Headache	17	77
Cold	34	63
Fever	18	78
Blood in stool	9	83
Breast lump†	2	96
Unusual vaginal bleeding or discharge†	1	93

*Percents do not total 100% owing to ambiguity of responses.
†Women only (n=99).

TABLE 4.—*Prevalence of Cigarette Smoking and Alcohol Consumption, Vietnamese and General US Population**

Smoking and Drinking Prevalence	Vietnamese, % Men (n = 116)	Women (n = 99)	US, % Men	Women
Current smokers	56	9	32	27
Former smokers	16	0	30	18
Never smoked	28	91	38	55
Current drinkers†	67	18	66	47
Heavier drinkers‡	13	2	10	2
Binge drinkers§	35	0	22	8

*Sources. US smoking: Pierce et al[22] and National Health Interview Survey, Office of Smoking and Health, unpublished data, 1987. US drinking: Behavioral Risk Factor Survey Surveillance System, Centers for Disease Control, unpublished data, 1987.
† ≥ 1 drink in past month
‡ ≥ 2 drinks per day in past month.
§ ≥ 5 drinks on ≥ 1 occasion in past month.

TABLE 5.—*Consumption of Indicator Foods Since Arrival in United States (n=215)*

Food Category	Respondents' Reported Consumption, % More	Some	Less
High fat			
Beef	73	17	10
Pork	57	25	18
Eggs	54	25	21
Cheese	48	48	4
High fiber			
Green vegetables	64	21	15
Fruit	68	19	13

food. From the six food categories, respondents reported a mean number of 2.59 (standard deviation 1.38) dietary changes toward food high in fat or low in fiber. A one-way analysis of variance showed that the younger the respondents, the more likely they were to make these changes. Those aged 21 to 34 (n = 98) made 2.89 changes, those aged 35 to 54 (n = 88) made 2.44 changes, and those aged 55 or older (n = 29) made 2.03 changes ($P < .01$). There was no relationship between sex and dietary change.

Cancer Screening

For each of five cancer screening tests, the respondents were more likely than the general US population to report that they had never had the procedure (Figure 1). For example, after interviewers explained the Pap test, 32% of the Vietnamese women reported that they had never had one compared with only 9% of women in the general US population.[17]

In addition, more Vietnamese were overdue for each of the five procedures than their US counterparts (Figure 2). Data for the Pap test show that 71% of the women surveyed were either overdue for or had never had a Pap test compared with 40% of women in the general US population.[17]

Age-eligible respondents whose regular physicians were Vietnamese were significantly less likely than those with non-Vietnamese physicians to have ever received a rectal examination ($P < .05$) or a stool occult blood test ($P < .05$). Women aged 34 or older (n = 47) were significantly more likely than younger women to have ever received a breast examination ($P < .05$), as might be expected. There were no significant associations, however, between respondents' screening status and income, type of health insurance, level of education, sex, number of years of residence in the United States, or knowledge of cancer.

Discussion

Despite the growing number of Vietnamese in the United States, there have heretofore been no studies regarding cancer prevention for this population. The data presented here show that among San Francisco Bay Area Vietnamese, cancer screening rates are low and important behavioral risk factors for cancer, especially cigarette smoking among men, are high. In addition, there are gaps in this population's knowledge about cancer and its risk factors.

Caution should be exercised, however, in generalizing from these findings to the population of San Francisco Bay Area Vietnamese as a whole. Although the sampling frame captured major segments of the population, it was not all-inclusive and, therefore, may not be representative. Although households were randomly selected, persons within these households were not. We think it is the more acculturated Vietnamese who more readily agreed to an interview. The direction of bias, therefore, should be toward underestimating the cancer prevention needs of this population.

In addition, the survey response rate (55%) was relatively low. Some respondents failed to keep scheduled interview appointments. Others might have agreed to an interview if they had been offered payment. Even more important in accounting for the low response rate may be the suspicion with which Vietnamese often regard outsiders—even of their own ethnicity. For Vietnamese, who have faced generations of warfare, avoiding strangers who ask questions has become an important survival skill.

All information about behaviors are based on self-reports, which may differ from actual behavior. Most of the findings cited here for US populations are also derived from reported behavior. Thus, the data presented here and the US data should be comparable. Finally, because of the small sample size, particularly for analyzing subsets of the data, point estimates are subject to sampling error.

Despite these limitations, however, to our knowledge this is the first comprehensive survey of cancer risks and screening among a randomly selected group of Vietnamese refugees in the US.

The most striking finding is the high prevalence of cigarette smoking among Vietnamese men. Although their level of consumption is moderate, it is of concern that nearly all smokers prefer cigarettes high in tar and nicotine, that many report one symptom of nicotine addiction (smoking soon after waking in the morning), and that most feel it would be difficult to quit. On the other hand, the profile of the male smoker that emerges from our data (the more recent, less acculturated refugee) may mean that as this population acculturates, smoking rates will decline and ap-

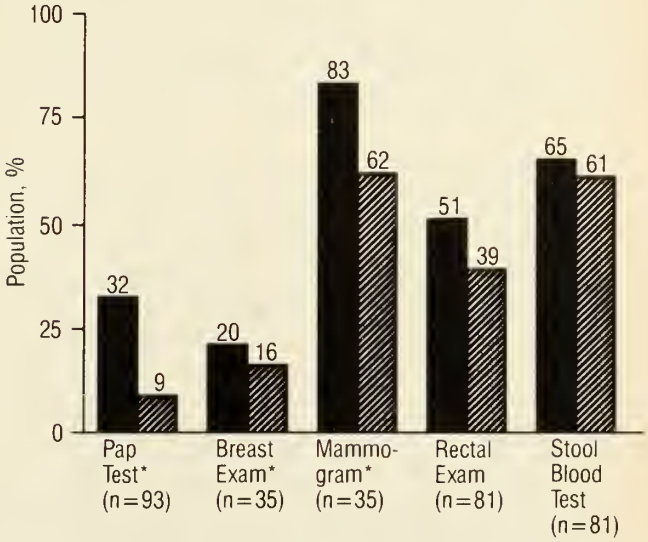

Figure 1.—Percent of population aged 40 years and older never having cancer screening procedures, Vietnamese and United States. ■ = Vietnamese; ▨ = US (from National Health Interview Survey, unpublished data, 1987); *=women only (Vietnamese Pap smear data for women 21 and older, US Pap smear data for women 18 and older)

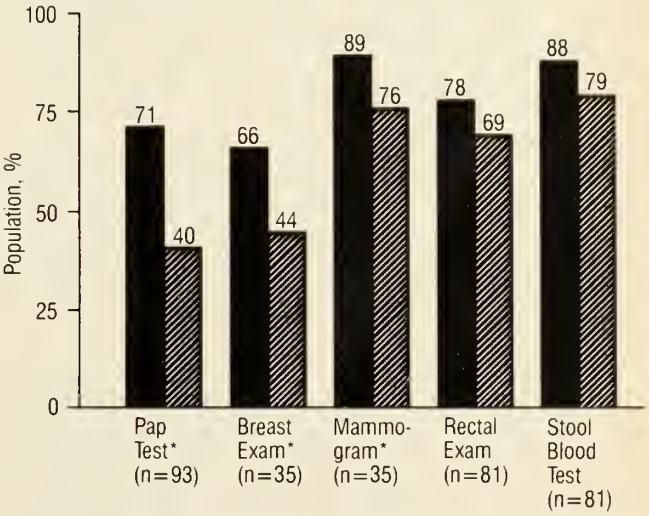

Figure 2.—Percent of population aged 40 years and older overdue (had cancer screening procedures > 1 year ago or never) for cancer screening procedures, Vietnamese and United States. ■ = Vietnamese; ▨ = US (from National Health Interview Survey, unpublished data, 1987); *=women only (Vietnamese Pap smear data for women 21 and older, US Pap smear data for women 18 and older)

proach those of the general US population. The fact that nearly all male former smokers have quit since arriving in this country adds weight to this supposition. Further research is needed to observe smoking prevalence trends and further characterize smoking behavior in this population.

When compared with the general US and California populations, there is little excess alcohol consumption among Vietnamese. Vietnamese women, in fact, drink at lower rates than their US counterparts. The excess rates of binge drinking reported by Vietnamese men, especially those aged 54 and older, indicate one subgroup that may be at higher risk.

The traditional Vietnamese diet is low in fat and high in fiber.[26] Survey respondents, however, reported that they are making food choices that raise the amount of fat and lower the amount of fiber in their diets. The dietary changes shown here may reflect the increased availability of food since arriving in the US. Our study shows, however, that dietary change is greatest in the more rapidly assimilating younger cohorts, which indicates that acculturation may also play a role. Although changes are evident in the diet, we do not know if the increased fat and decreased fiber consumption reaches levels linked to increased cancer morbidity.

Although hepatitis B prevention has become a priority in a number of public health agencies in the United States, the Centers for Disease Control report that only 2% of the Southeast Asian refugees in this country have been immunized.[27] In addition, programs that identify high-risk pregnant women who are positive for HBsAg are not always successful in gaining compliance from patients in completing the series of immunizations for their infants.[28] Our study, which shows a low awareness of the issue of hepatitis B in the Vietnamese community, indicates that culturally appropriate education about hepatitis B is needed to improve compliance with immunoprophylaxis programs.

We suspect that the low cancer screening rates observed here reflect lower levels of cancer screening in Vietnam. There may also be barriers in this country that reduce access to the health care system and that might contribute to these low rates.

Although nearly half the persons interviewed reported limited English-language proficiency, this factor was not a barrier to health care access as Vietnamese physicians and translators were widely available. Language may pose a barrier to Vietnamese living in other parts of the United States, however, where language-appropriate health care services may not be available.

The use of traditional medical practices did not appear to pose a barrier to seeking appropriate Western medical treatment of symptoms of cancer. The data show that a belief in and the use of both medical systems coexist. More study of actual rather than self-reported behavior is needed to further clarify to what extent traditional medical practices may cause a delay in seeking Western medical treatment.

Our findings indicate that Vietnamese are seeking physicians and that opportunities for screening do exist. Fewer respondents reported no visit to a physician during the past year compared with the US population (12% versus 24%).[29] Because most respondents rated their health as "fair" or "poor," however, it is reasonable to assume that visits were not made for preventive care. Finally, respondents had a rate of health insurance coverage comparable with that of the general US population (85% versus 87%).[30]

Because respondents with Vietnamese physicians had lower rates of rectal examinations and stool occult blood tests, Vietnamese cultural considerations may pose barriers to some cancer screening. It has been widely reported that Vietnamese patients, especially women, are reluctant to disrobe for a physical examination.[18,21,31,32] It is possible that, together, Vietnamese patients' resistance and Vietnamese physicians' deference to patients' modesty may create a barrier to the performance of these tests.

The National Cancer Institute has set a goal of reducing cancer mortality in the United States by as much as 50% by the year 2000.[3] Minority populations, such as the Vietnamese, should not be left out of cancer prevention efforts. The data presented here should alert the public health community to the cancer prevention needs of the Vietnamese refugee population in this country. High priorities for the Vietnamese should include education about cancer and its risks and prevention, education about hepatitis B and its prevention, and programs to promote smoking cessation, moderation of alcohol intake, dietary modification, and cancer screening.

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Articles

Outcome, Transport Times, and Costs of Patients Evacuated by Helicopter Versus Fixed-Wing Aircraft

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We determined the differences in transport times and costs for patients transported by fixed-wing aircraft versus helicopter at ranges of 101 to 150 radial miles, where fixed-wing and helicopter in-hospital transports commonly overlap. Statistical analysis failed to show a significant difference between the trauma-care patients transported by helicopter (n = 109) and those transported by fixed-wing (n = 86) for age, injury severity score, hospital length of stay, hospital mortality, or discharge disability score. The times in returning patients to the receiving hospital by helicopter (n = 104) versus fixed-wing (n = 509) did not differ significantly. Helicopter transport costs per mile ($24), however, were 400% higher than those of fixed-wing aircraft with its associated ground ambulance transport costs ($6). Thus, helicopter transport is economically unjustified for interhospital transports exceeding 100 radial miles when an efficient fixed-wing service exists.

(Thomas F, Wisham J, Clemmer TP, et al: Outcome, transport times, and costs of patients evacuated by helicopter versus fixed-wing aircraft. West J Med 1990 Jul; 153:40-43)

The development of major trauma referral centers has had a positive effect in improving the outcome for severely injured patients.[1-3] To be effective, these centers must care for a large number of critically injured patients.[4] Field triage systems have been developed allowing patients who would benefit from care given at a major trauma center to be rapidly identified and transported directly to these facilities.[5-7]

Recently there has been a rapid growth in helicopter and fixed-wing aeromedical programs.[8,9] Aeromedical transport allows the rapid transport of severely injured patients and increases accessibility to needed tertiary care services.[10,11] Frequently the areas served by fixed-wing and helicopter aeromedical transport services overlap. The benefit of the helicopter is that it allows rapid liftoff from the hospital to the scene of injury without the required ground transport associated with fixed-wing transports. The benefits of the fixed-wing service are a faster air speed, longer distances that can be traveled without refueling, greater weather capabilities, lower operating costs, and a better safety record.[12]

Despite proclaimed advantages or disadvantages of helicopter versus fixed-wing transports, the question remains whether the use of helicopter or fixed-wing aircraft to transport patients from similar distances makes a difference in outcome, transport times, or transport costs for patients referred to a major trauma-care center. To date, there are no published studies that have attempted to make this comparison.

Methods

The study hospital is a level I trauma center that operates a helicopter and fixed-wing aeromedical transport service. Two fully dedicated fixed-wing air ambulances are staffed by pilots on site 24 hours a day at a local airport. A flight nurse or physician and an intensive-care-unit nurse make up the on-call team for fixed-wing transports. The fixed-wing, twin-turbine engine, pressurized aircraft (MU-II) averages 340 miles per hour (mph). A fully dedicated single-engine turbine helicopter (Alouette III) is based at the hospital with an on-site pilot, flight nurse, and flight paramedic. The average speed of the helicopter is 115 mph.

In an attempt to delineate any difference in outcome occurring because of the mode of transport (fixed-wing versus helicopter), we compared the cases of all trauma-care patients aeromedically transported from May 1979 through December 1987 who were transported from similar distances to the same level I trauma center. Trauma-care patients were selected because a variety of physiologic and anatomic scores have been developed that would allow for a determination of any differences in injury severity between patients transported by helicopter versus fixed-wing aircraft.[5-7,13] For the study, the trauma-care patients were stratified by transport distance into six groups starting with those transported 75 radial miles or less and increasing by 25-radial-mile increments, with the final group representing patients transported more than 175 radial miles to the study hospital.

The six groups were further condensed into three groups based on distances in which the helicopter was predominantly used ($\leq$ 100 radial miles), helicopter and fixed-wing usage was similar (101 to 150 radial miles), and fixed-wing transport was predominantly used ($>$ 150 radial miles). The trauma-care patient groups were then compared by age, injury severity score, hospital length of stay, hospital mortality, and discharge disability score (Table 1).[14]

Following the trauma patient outcome results, transport times for fixed-wing versus helicopter transports for all patients—cardiac, medical, trauma care, obstetric, and pediatric—transported between January 1, 1985, and December 15, 1988, at distances of 101 to 150 radial miles were analyzed. The time of aircraft liftoff was determined from the time the first requesting call was received by the dispatch center until the aircraft first lifted off from either

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the airport (fixed-wing) or the hospital (helicopter). The return time was determined from the time of the first requesting call to the dispatch center until the patient arrived at the destination hospital. Only emergency transports were evaluated. Elective medical transports or those that were delayed because of weather were excluded from the analysis. Ground transport time from the airport to the receiving hospital was included in the total fixed-wing transport times.

Finally, to determine cost differences between helicopter versus fixed-wing transports, the true transport costs per mile of fixed-wing aircraft versus helicopter were calculated for all transports in 1987. The costs included both the direct and indirect costs of all leases, overhead, personnel, equipment, dispatch, fuel, maintenance, medications, and supplies, and a cost per mile to transport patients by helicopter versus fixed-wing aircraft was calculated. A standard ground ambulance transport cost of $370 for transfers between the referring and receiving hospitals and their local airports was incorporated into the costs for fixed-wing transports.

Statistical data are reported as absolute numbers and mean plus or minus standard deviations. All results were tested statistically using the unpaired *t* test and the χ^2 analysis. Data analysis was considered significant when a *P* value of less than .05 was obtained.

Results

During the study, 660 trauma-care patients were transported by helicopter and 266 trauma-care patients by fixed-wing aircraft. The average injury severity score for the patients transported by helicopter (23.1 ± 15.6) was not significantly different from those of patients transported by fixed-wing aircraft (22.8 ± 14.2). No patient died during transport. Only 1 patient was transported by fixed-wing less than a 75-mile radius, and 510 patients were transferred by helicopter at this range (Table 2). Most patients transported less than 75 miles were transferred by helicopter directly from the accident scene to the referral trauma center. All fixed-wing and helicopter transports greater than 75 radial miles were done as interfacility transports because at this distance it is in the patient's best interest to be first ground-transported to the nearest facility for initial stabilization. For all six groups defined in 25-mile increments (Table 2) and for the three consolidated groups (Table 3), no statistical differences were found between trauma patients aeromedically evacuated by helicopter versus fixed-wing for age, injury severity score, length of hospital stay, hospital mortality, or disability discharge score. Helicopter and fixed-wing transports were commonly found to overlap in the 101- to 150-radial-mile range (Table 3).

We found that for all 613 trauma and nontrauma patients transported at 101 to 150 radial miles, fixed-wing

TABLE 1.—*Discharge Disability Score*

Score		*Definition*
1	Death	
2	Severe disability (complete dependency)	Patients who because of the injuries sustained are dependent on others for even their basic needs such as eating, dressing, and toilet duties
3	Moderate disability (disabled but independent)	Patients who because of the injuries sustained are dependent on others or mechanical devices to carry out more complex but routine daily activities such as climbing, driving, or performing more delicate physical or mental tasks
4	Minor disability	Patients who because of the injuries sustained have persistent minor limitations or complaints but are able to function completely independently and carry out a normal life-style
5	Normal	Patients who are functioning at their preinjury level without limitation or complaints

TABLE 2.—*Clinical Characteristics and Distances Traveled, in 25-Mile Increments, of Trauma Patients Requiring Helicopter (n=660) Versus Fixed-Wing (n=266) Aeromedical Transport**

Transport Distance, Miles	*Patients, No.*	*Age, years*	*Injury Severity Score*	*Hospital Length of Stay, d*	*Hospital Mortality, %*	*Discharge Disability Score†*
<75						
Helicopter	510	30.2±13.7	23.6±15.4	12.5±14.3	57	3.4±1.3
Fixed-wing	1	21	18	6.7	0	3
76-100						
Helicopter	33	29.1±12.1	23.3±13.0	13.4±13.9	6	3.2±1.3
Fixed-wing	16	31.9±17.2	27.7±13.6	16.6±13.3	1	3.2±1.3
101-125						
Helicopter	85	29.7±11.7	19.7±17.0	8.8± 7.8	5	3.9±1.1
Fixed-wing	28	28.8±10.0	18.7±10.2	12.2±12.0	1	3.6±1.0
126-150						
Helicopter	24	25.4±15.1	24.3±15.6	15.7±16.3	4	2.9±1.3
Fixed-wing	58	32.6±15.5	23.5±17.5	11.1±12.5	6	3.5±1.2
151-175						
Helicopter	5	34.6±16.2	25.6± 9.8	15.2± 9.0	0	3.5±1.2
Fixed-wing	76	30.8±12.7	24.5±14.2	12.2±11.7	10	3.0±0.7
>175						
Helicopter	3	22.7± 1.5	33.3±29.4	8.3±10.2	0	4.0±1.7
Fixed-wing	87	32.9±15.1	21.4±12.9	13.0±12.8	8	3.4±1.2

*Except for those of the patient requiring fixed-wing transport of a distance of <75 miles, all values are given as the mean±standard deviation.
†At time of hospital discharge. See Table 1 for the definition of Discharge Disability Score.

TABLE 3.—*Clinical Characteristics and Distances Traveled, in 50-Mile Increments, of Trauma Patients Requiring Helicopter (n=660) Versus Fixed-Wing (n=266) Aeromedical Transport**

Transport Distance, Miles	*Patients, No.*	*Age, years*	*Injury Severity Score*	*Hospital Length of Stay, d*	*Hospital Mortality, No.*	*%*	*Discharge Disability Score†*
0-100							
Helicopter	543	30.2±13.6	23.6±15.3	12.5±14.3	63	(12)	3.2±1.3
Fixed-wing	17	31.3±16.8	27.1±13.4	19.4±17.8	1	(6)	3.2±1.2
101-150							
Helicopter	109	28.8±12.6	20.7±16.7	10.2±10.5	9	(8)	3.7±1.2
Fixed-wing	86	31.4±14.0	21.9±15.6	11.4±12.3	7	(8)	3.6±1.2
>150							
Helicopter	8	30.1±13.8	28.5±17.8	12.6± 9.4	0	(0)	3.3±1.2
Fixed-wing	163	31.9±14.0	22.9±13.6	12.6±12.2	18	(11)	3.4±1.3

*All values given as the mean±standard deviation.
†At time of hospital discharge. See Table 1 for the definition of Discharge Disability Score.

TABLE 4.—*Times, in Minutes, of Helicopter Versus Fixed-Wing Aeromedical Transport of Trauma and Nontrauma Patients*

Transport Distance, Radial Miles	*All Patients, No.*	*Helicopter**	*Fixed-Wing**	*P Value*
101-150				
Patients, No.	613	104	509	...
Miles	127	112±13	130±13	<.001
Age, years	37	40±27	36±27	.107
Liftoff time, min†	41	22±14	45±17	<.001
Return time, min‡	204	197±32	205±79	.099
101-125				
Patients, No.	271	84	187	...
Miles	113	107± 6	115± 4	<.001
Age, years	39	41±27	38±25	.327
Liftoff time, min†	39	21±12	46±17	<.001
Return time, min‡	194	189±27	196±69	.250
126-150				
Patients, No.	342	20	322	...
Miles	139	136± 6	139± 9	.101
Age, years	35	38±24	35±28	.595
Liftoff time, min†	44	28±22	45±17	.004
Return time, min‡	211	230±28	210±83	.014

*Values, except number of patients, given as the mean±standard deviation.
†Time from first requesting call to dispatch to the time aircraft lifts off
‡Time from first requesting call to dispatch to the time patient arrives at receiving hospital.

TABLE 5.—*Speed, Travel Time, and Costs per Mile of Emergency Medical Service (EMS) Helicopters**

		Time of Travel, min		
EMS Helicopters	*Speed, mph*	*100 Miles*	*150 Miles*	*Cost/Mile, $†*
Alouette III	115	52	78	10.47
Long Ranger L-3	126	48	71	11.59
Astar	144	42	62	9.65
Twin Star	145	41	62	13.56
BO-105	151	40	60	13.35
Agusta 109A	169	36	53	15.54
BK-117	160	38	56	18.47
Bell 222UT	163	37	55	16.70
Dauphin	176	34	51	24.22
S-76	167	36	54	24.66
Bell 212	115	52	78	22.83
Bell 412	141	43	64	26.24

*Adapted from *The 1983 Aeromedical Helicopter Evaluation, First Edition*, with permission.[20]
†These cost figures are for aircraft operations only and do not include medical personnel or equipment costs.

(n = 509) and helicopter (n = 104) transport times were equal in returning patients to the receiving hospitals. Mileage subgroup comparisons showed that there was no difference between helicopter versus fixed-wing in transporting a patient to the receiving hospital in the 101- to 125-mile range. In the 126- to 150-mile range, however, fixed-wing transport was found to be significantly ($P = .014$) faster than helicopter by nearly 20 minutes in transporting the patient to the receiving hospital (Table 4).

Analysis of the cost per mile of fixed-wing versus helicopter transport indicates that the calculated true helicopter costs ($24 per mile) were 400% higher than the true cost of the fixed-wing aircraft and associated ground ambulance charges ($6 per mile).

Discussion

The number of aeromedical transport services has grown dramatically within the past decade. These systems allow critically ill and injured patients to rapidly receive needed life-saving services. In recent years, helicopter aeromedical transport service has come under considerable criticism as being a costly and uneconomic means of delivering health care services.[15] Further, the recent rash of aeromedical helicopter crashes has spurred public concern as to the safety of these services.[16,17] The "Health Policy Agenda for the American People for the Assessment of Health Care Technology" declared,

> The primary goal of the assessment process should be the evaluation of the safety, efficacy, and conditions of use of existing and new health care technologies. Evaluations of the cost-effectiveness of such technologies should also be conducted. . .[18(p1207)]

To this end, our study evaluated the efficacy and cost-effectiveness of helicopter versus fixed-wing aeromedical transports.

We found that at ranges of 101 to 150 radial miles, the outcome for severely traumatized patients as determined by mortality, hospital length of stay, and discharge disability score was not affected by the type of aeromedical transport (helicopter versus fixed-wing). Furthermore, it appears that at this distance range, fixed-wing aircraft is comparable to (101 to 125 radial miles) or faster (126 to 150 radial miles) than helicopters in returning patients to tertiary care treatment centers. Despite these similarities, the study did find that the cost of transporting patients by helicopter is 400% higher than the cost of transporting patients by fixed-wing.

When the accident rates of turbine helicopters are compared with those of fixed-wing turbine aircraft in general aviation, the accident rate for the twin-turbine fixed-wing aircraft is about 25% less than that of a single-turbine helicopter and nearly 50% less than a twin-turbine helicopter.[12] Given that there is no difference in trauma patient outcomes between helicopter and fixed-wing aeromedical transport, that the accident rates are less with fixed-wing versus helicopter transport, and that rotor-wing transport cost is four times that of fixed-wing, rotor-wing transports may be economically unjustified for the interhospital transport of trauma patients more than 100 miles when a medically comparable fixed-wing service is available.

Although the argument can be made that a faster twin-engine rotor-wing aircraft could reduce the travel time from that of the single-turbine engine helicopter used in this study (Table 5), additional analysis shows that except for one helicopter, the use of other faster helicopters would likewise increase the operating costs by 10% to 150%.[19,20] The use of fixed-wing aeromedical services may not be applicable to all regions because of the close proximity of patient transports (< 100 radial miles) or the accessibility of sufficient airport runways. Aeromedical helicopter transport programs that frequently fly distances of more than 100 radial miles, however, should consider the development and use of efficient fixed-wing transport services to reduce patient care costs and enhance helicopter availability.

In the final analysis, it must be the responsibility of referring physicians to assure that their patients who require emergency transport not only receive quality medical care, but that the selected mode of transport has been maximized in terms of safety and cost-effectiveness. Further studies should now be done to determine the medical efficacy and cost-effectiveness of helicopter versus ground ambulance transport of patients transported from similar distances. Only through such studies can the safety, efficacy, cost-effectiveness, and proper use of medical transport services be determined.

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Articles

The Physician as a Patient Educator
From Theory to Practice

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Patient nonadherence to therapeutic regimens is a serious issue in the practice of medicine. Empiric studies done by professionals from diverse backgrounds have shown that physicians who use educational strategies can be effective in gaining the cooperation of patients to follow their recommendations. The educational model that currently is most familiar to physicians and the one they use most frequently when educating patients is pedagogy, the theoretic basis for teaching children. Andragogy, a theoretic basis for teaching adults, is now being suggested by medical educators as an alternative model. To illustrate the clinical relevance and application of the andragogic approach, studies focusing on physician behaviors associated with behavioral measures of adherence were reviewed, analyzed, and categorized according to a framework called the "ADULT" model. Physicians in a postgraduate training program who have had exposure to this framework and have incorporated it into their practices report less difficulty functioning as patient educators. The systematic use of this approach can have a positive effect on patient adherence.

(McCann DP, Blossom HJ: The physician as a patient educator—From theory to practice. West J Med 1990 Jul; 153:44-49)

Estimates of patient nonadherence to physicians' therapeutic recommendations range from 50% to 92%.[1] Reviews of empiric studies have repeatedly emphasized the magnitude and pervasiveness of this problem,[2,3] and recently Haynes[4] identified it as one of the most important issues medical practitioners face today.

To identify the factors affecting patient nonadherence, the physician-patient relationship has been studied extensively over the past three decades by physicians, psychologists, sociologists, educators, and anthropologists. While some investigators have analyzed the dyadic relationship from broad philosophic and sociologic perspectives,[5-8] others have examined the behavioral interactions that take place between patients and their physicians.[9-36] Initially the emphasis of the interactional research was on patient behavior, but attention gradually shifted to physician behavior and its role in this complex exchange. We will examine the research related to physician behavior.

The accumulated data supporting physician interactive behaviors and their positive effect on patient adherence are extensive. While these physician behaviors are often characterized by investigators as interpersonal skills in interviewing, communication, or instruction-giving, they are also regarded as educative because they are all means of facilitating decision making that enhance the likelihood of behavior change on a patient's part.

According to Brunton,[37] the educational theory most familiar to physicians and the one they use most frequently when educating patients is pedagogy. This theoretic framework refers to a body of knowledge that forms the basis of teaching children. Medical educators are now suggesting that andragogy, an adult learning theory described by Malcolm Knowles,[38,39] be considered as an alternative conceptual framework because the majority of patients are adults and because the results of adherence research confirm the usefulness of this approach.[37,40]

Based on well-recognized conditions of learning and principles of teaching adults, andragogy differs from pedagogy primarily in its central premise regarding the teacher-learner relationship. In the pedagogic model, the relationship between the teacher and learner is based on authoritative expertise. The teacher's role is to determine the nature and scope of the educational program and then to instruct the passive, cooperative learner. In the andragogic model, the teacher-learner relationship is one of mutual participation. The teacher's role is to facilitate, promote, and encourage the learner's active involvement in developing and planning the educational program.

Although medical educators are suggesting that physicians consider using the andragogic approach to patient education, the clinical application of this theoretic framework has yet to be described in the literature. The purpose of our report is to illustrate how the full range of physician behaviors associated with improved patient adherence can be applied to the clinical setting within the context of an adult learning theory.

We review here 28 investigations of the physician-patient relationship that have established a positive association between specific physician interactive behaviors and behavioral measures of patient adherence. A total of 46 physician behaviors were identified. After analyzing their relevance to andragogy, it was possible to categorize these generic behaviors into the five basic steps of the educational process that parallel the usual sequence of activities of the physician-patient interview: step 1: establish rapport; step 2: assess needs; step 3: develop a plan; step 4: implement the plan; and step 5: evaluate the plan.

Clinicians, continually pressed with the medical aspects of the interview and ever mindful of time, are not expected to carry out each of these behaviors at every patient visit. Rather, it is the conceptual premise of active patient involvement in each step of the educational process that is crucial. The use of specific physician behaviors is expected to vary from time to time depending on circumstances. The

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following guidelines for implementation have been developed around the mnemonic, ADULT:

Guidelines for Physician-Patient Education

A Establish rapport by eliciting patient's
Active involvement
D Assess needs by listening carefully as patient
Discusses concerns
U Develop a plan by promoting an
Understanding of the issues
L Implement the plan by offering patient opportunities to
Learn new behaviors
T Evaluate the plan by identifying strategies for
Tracking patient's progress

Review of the Literature

Step 1: Establish Rapport

A summary of the studies that document the importance of physicians developing agreeable relationships with patients is given in Table 1. Several studies illustrate this theoretic construct.[9,11,12,18,19,23,35]

One of the first researchers to identify the value of a caring attitude on the part of the physician, Alpert did a causal-comparative study of appointment-keeping behaviors of 1,588 patients attending Boston Children's Hospital Medical Center Outpatient Department.[9] Of those who kept their appointments, 77% generally agreed that their physicians were interested in them as patients, as compared with only 54% of those who did not keep their appointments.

In his descriptive study of 119 new patient-physician visits and 104 follow-up visits of the same patient-physician dyads, Davis discovered that providing opportunities for patients to release tension enhanced patient adherence.[11,12] He concluded his report by emphasizing the importance of establishing rapport with patients to "build commitment to the relationship so that ultimately the patient will follow advice," a finding later substantiated by other researchers.[10,18,35]

Korsch and associates studied 800 acutely ill children brought for a first visit to the emergency clinic at Childrens Hospital of Los Angeles.[23] Analyzing data derived from tape recordings of the physician-parent or child interaction and two follow-up interviews with the parents, Korsch and co-workers discovered that parents who identified physicians as courteous, friendly, and personable were more likely to follow medical advice than were parents who perceived the physicians as businesslike, inattentive, and uncaring.[23] Interest, empathy, and concern of physicians toward their patients were also associated with higher rates of adherence. As part of the same study, Freemon and colleagues analyzed the content of 285 of the visits and found that the greater the degree of physician friendliness, the more likely the patients were to comply with advice.[18] While Korsch, Francis, and Freemon and their co-workers did not claim that physician warmth alone affected adherence, they did report that a blatantly unpleasant manner on the physician's part adversely affected patient cooperation.

Stewart assessed whether patient-centered interviews encouraging active patient involvement were related to patient satisfaction and adherence.[35] In a causal comparative study of office visits of 24 Canadian family physicians, 140 patient visits were audiotaped and their content analyzed using Bales Interaction Process Analysis.[41] A bivariate analysis showed that patient-centered interviews were related to significantly higher reported adherence.

A study done by Greenfield and associates in 1985 illustrates the benefits of encouraging patients to be actively involved in physician-patient interactions.[19] At Veterans Administration Medical Center, 45 outpatients with peptic ulcer disease were randomly assigned to experimental or control groups. The experimental intervention, consisting of an individualized 20-minute educational session just before their visit with their physician, focused on assisting them in identifying relevant medical decisions warranting discussion with their physicians according to a preestablished algorithm. Assertive techniques patients could use to overcome barriers to discussing identified issues with their physicians were reinforced. After the visit with the physician, the experimental group received copies of the algorithm and their medical record. The control group received only a session of comparable length that focused on reviewing a standardized protocol. Statistical analysis of the data showed that patients in the experimental group had a greater degree of involvement and assertiveness in their interactions with physicians and reported fewer physical limitations, less pain, and an increased preference for active involvement in the medical decision-making process than did their counterparts in the control group. Furthermore, these effects were achieved in a veteran population, one that is characteristically older, more entrenched in the pedagogic style, and less likely to be assertive in medical decision making.

Step 2: Assess Needs

Several studies identify physician behaviors related to the second step of the educational process (Table 2). A few have been selected for discussion purposes.[15,22,23,26,28,29]

In the previously mentioned study involving pediatric patients, Korsch and associates found that physicians who identified the main concerns of the patients' parents were more likely to enlist their cooperation during subsequent visits.[23] Of 625 parents who said their physicians understood their concerns, 83% expressed satisfaction and ad-

TABLE 1.—*Step 1: Establishing Rapport*

Physicion Behovior	*Source**
Act in courteous, friendly manner	18, 23, 35, 36
Show interest, empathy, concern	9, 13, 17, 18, 23, 35
Provide opportunities for release of patient tension	10, 11, 12, 18, 35
Encourage active involvement of patient	15, 19, 22, 25, 29, 30, 31, 33, 34, 35
Communicate in language patient can understand	9, 23
Listen attentively to patient	23, 26
Show sensitivity to psychosocial issues	24, 29

*Numbers refer to those in list of references at end of article.

TABLE 2.—*Step 2: Assessing Needs*

Physicion Behovior	*Source**
Identify patient concerns, issues	15, 17, 22, 23, 28, 29, 33, 34, 35
Explore patient's knowledge of issue	22, 24, 25, 26, 29
Explore patient's attitudes, beliefs about issue	22, 25, 26
Explore patient's attempts or skills in dealing with issue	22, 24, 25, 29
Explore patient's level of motivation or ability to change	22, 25
Identify patient's strengths and limitations	22, 24, 29

*Numbers refer to those in list of references at end of article.

hered to the regimen prescribed for their child, but of the 80 parents who perceived their child's physician as not understanding their concerns, only 32% expressed satisfaction and were cooperative.

In his report of a quasi-experimental study involving 100 outpatients with congestive heart failure, Rosenberg further showed the importance of a needs assessment.[29] The 50 patients in the experimental group were routinely interviewed by their physicians and other health care team members to identify their perceived needs, concerns, and worries. These data were used to plan interventions that led to a reduced number and duration of hospital admissions and enhanced other measures of improved health status.

Eisenthal and associates also studied the effects of eliciting, hearing, and understanding patient requests and subsequently using these requests as a basis for formulating a treatment plan with patients.[15] In a prospective study, they examined the effect of this kind of "negotiated" approach with 300 new patients attending an acute psychiatric service. Half of the patients were seen by physicians trained to use the negotiated approach, while the other half were assigned to a control group whose physicians used the "traditional" diagnostic approach. Patients in the experimental group were much more likely to adhere to the treatment plan than were those in the control group.

Similar findings were reported by Orth and colleagues in a study of 217 hypertensive patients visiting one of nine physicians in four community health centers in Houston, Texas.[28] The interactions were analyzed using a taxonomy of verbal response modes.[42] The results showed a positive correlation between the patients' expressions of their concerns, worries, or reasons for seeking treatment and improvements in blood pressure.

In a study done by Inui and colleagues in 1976,[22] physicians were taught how to explore their hypertensive patients' level of knowledge, health beliefs, and adherence behaviors. The physicians were also taught to use this information to develop individualized patient education interventions. Patients in the experimental group showed consistently improved adherence and better blood pressure control than did patients in the control group.

In a study carried out in the Department of Medicine at the University of California, Los Angeles, Linn and Wilson reviewed the needs assessment approach used by 76 interns and residents with their patients who were scheduled for clinic visits.[26] They found that physicians in the general clinic who had been trained to explore patients' thoughts and feelings in a nonauthoritarian manner and who used a facilitating rather than a nonfacilitating response had lower "no-show" rates than did physicians from the regular clinic who lacked this training. Personal telephone cancellation rather than unexplained appointment breaking was also significantly higher for the first group. While the authors concluded that good interpersonal skills alone are not sufficient to effect improved adherence with follow-up visits, they stressed that the communication style of the health care provider can certainly make a difference in patients' follow-up patterns.

TABLE 3.—*Step 3: Developing a Plan*

Physicion Behavior	*Source**
Address patient's concerns, issues	22, 23, 29, 33, 34, 36
Explain findings of examinations, tests, x-ray films	16, 19, 29
Inform patient of diagnosis, conclusions	16, 17, 18, 19, 23, 25, 29
Explain cause of problem	16, 17, 23, 28
Explain prognosis, implications	16
Express concern about patient's behavior	25
Explain benefits of changing behavior	25
Identify decisions that need to be made	19
Elicit patient involvement in decision-making process	15, 19, 24
Inform patient of treatment options, consequences	15, 19, 25
Elicit treatment preferences of patient	15, 19, 22, 29, 35
Recommend treatment plan to patient	11, 12, 17, 19, 22, 23, 25, 29, 32, 33, 34, 36
Provide rationale for choice of treatment	19, 22, 36
Attempt to resolve patient-physician differences	15, 19, 22, 29

*Numbers refer to those in list of references at end of article

Step 3: Develop a Plan

Table 3 delineates physician behaviors related to developing a plan with patients. At this step physicians collate the derived needs of patients with their professional assessments of the situation into a therapeutic plan for the patients' consideration. Numerous reports illustrate this concept.[15,17,19,23,32-34]

Korsch and co-workers noted that one of the highest rates of dissatisfaction mentioned during follow-up interviews with parents occurred in those visits where the main concerns of the parents remained unaddressed.[23] Starfield and associates also emphasized the importance of considering patients' concerns as an essential step in the process of care.[33] In a study designed to examine the effects of greater patient participation in the interview process, the authors found that follow-up adherence was better for those issues for which both patient and physician had agreed on the necessity of follow-up care. Increased patient participation was also associated with an overall improvement in health status. Of the recognized problems that were listed jointly, 63% were reported as improved as compared with 22% of those listed by patients only. A second study of a similar nature by Starfield and colleagues on a separate sample of patients confirmed the findings of the earlier study.[34]

In their analysis of tape recordings gathered during 800 new-patient pediatric visits, Francis and associates discovered that when physicians provided feedback by explaining the diagnosis and its cause, patient adherence increased.[17] Mothers who expected to learn the cause and nature of their child's illness and failed to do so were less likely to follow medical advice than were those whose expectations were met.

In their study of patients with peptic ulcer disease, Greenfield and co-workers found that identifying decisions that needed to be made and encouraging patients to become involved in the decision-making process had a positive influence on patients' adherence.[19] They also noted that informing patients of treatment options and their consequences and identifying patients' treatment preferences proved beneficial.

Russell and associates did a study that shows the influence of physicians' recommendations on patient adherence.[32] The researchers randomly assigned 2,138 cigarette-smoking patients of 28 general practitioners in five group practices in London to one of four groups: nonintervention control, questionnaire only, advice by their physician to stop smoking, and counseling and specific written information designed to facilitate smoking cessation. Physician education emphasized motivating patients to make specific behavioral intentions and commitments to stop smoking.

The results showed a positive linear relationship between the strength of the interventions used and the patient's ability to stop smoking. Patients who received both counseling and written materials achieved the greatest reduction in smoking of all groups, with 5.1% still not smoking after a year of follow-up. This compared with 3.3% for the advice-only group, 1.6% for the questionnaire-only group, and 0.3% for the nonintervention control group.

As mentioned earlier, Eisenthal and co-workers studied the effects of using patients' requests as a basis for formulating treatment plans.[15] Patients in the experimental group whose requests were used to "negotiate" a treatment plan were much more likely to adhere to it than were those in the control group. The investigators concluded that the experimental approach served to validate patients' ideas and predispose them toward greater participation in developing their treatment plans.

Step 4: Implement the Plan

Table 4 summarizes the research findings associated with implementing the educational plan. Three approaches to implementation have been identified: individualized instruction, or one-on-one instruction of patients by their personal physicians; instruction that is adjunctive in nature, or that which is done by other health professionals under the supervision of the patient's personal physician; and referral to an educational program designed for a specific patient population. We focus on the first two approaches.

Individualized instruction. Many researchers have reported positive outcomes of one-on-one physician instruction of patients, and this is the most frequently used physician implementation strategy to effect behavior change. A few representative studies have been selected for discussion.[22,24,36]

The importance of physician instruction is illustrated by Svarstad's study involving 153 adult black and Puerto Rican patients seen by eight physicians at a neighborhood health center in an urban ghetto.[36] A content analysis of transcripts showed that patient conformity was higher when physicians had been friendly but authoritative (not authoritarian) and instructive. Giving explicit instructions and emphasizing important issues were also associated with higher rates of adherence.

TABLE 4.—*Step 4: Implementing the Plan*

Physician Behavior	*Source**
Exert authority	11, 12, 36
Reinforce healthy behaviors, beliefs of patient	19, 20, 22, 25, 29
Simplify treatment regimen	17, 21
Tailor treatment regimen to patient	14, 19, 20, 21, 22, 23, 24, 25, 29
Organize instruction	19, 20, 24, 25, 29
Provide adequate amount of relevant information	14, 18, 19, 20, 24, 25, 28, 29
Instruct patient on specific skill	10, 14, 20, 21, 22, 24, 25, 29, 36
Emphasize important points	19, 20, 24, 29, 36
Provide opportunity to practice skill	14, 19, 24
Supplement discussion with handouts	19, 20, 24, 25, 29, 32
Encourage patient to use family or social supports	24, 25, 27, 29
Summarize major points	25

*Numbers refer to those in list of references at end of article.

As mentioned earlier, Inui and colleagues conducted a study of physicians treating patients for hypertension.[22] In this study, 29 physicians assigned to the experimental group were taught to explore their patients' level of knowledge, health beliefs, and adherence behaviors and to use the assessment information in designing interventions for their patients. The 33 physicians in the control group used the traditional approach to patient interviews. Outcomes of the study showed that physicians in the experimental group spent more time providing patients with relevant information and instruction on specific self-care skills, with the result that their patients showed improved understanding, satisfaction, adherence, and blood pressure control as compared with patients of control group physicians.

In a study directed by Levine and Britten, 45 patients with hemophilia were individually instructed by their physicians in the management of their bleeding disorders.[24] Patients and members of their immediate families received organized instruction consisting of a combination of cognitive and skill-building strategies. Data collected during 12 months of the program were compared with data collected from the previous year, so that patients served as their own controls. The investigators found reductions of 74% in the amount of absenteeism, 89% in the number of days in hospital, 76% in the number of outpatient visits, and a 45% decrease in health care costs for the year in which the experimental instruction was given. The authors recommended that this type of individualized teaching by physicians could be used as a model in treating patients with other chronic illnesses.

Adjunctive instruction. Egbert and colleagues were among the first investigators to report the positive effects of adjunctive patient instruction by members of an interdisciplinary health team.[14] A total of 98 surgical patients admitted to the Massachusetts General Hospital (Boston) for an elective intra-abdominal operation were randomly selected for experimental and control groups. Those in the experimental group received a combination of cognitive, motivational, and skill-building education and reinforcement from the anesthesiology and nursing staffs. The patients in the control group received the usual presurgical care. Patients in the experimental group requested 50% fewer narcotics for the relief of postoperative pain and were ready for hospital discharge 2.7 days earlier than were patients in the control group.

Rosenberg also reported the value of a team approach to patient education as an adjunct to personal physician education through regular physician visits.[29] In this study, patients in the experimental group and their family members participated in self-help support sessions involving discussions with physicians, nurses, dietitians, and social workers. This group had more positive health outcomes than did members of the control group as measured by hospital readmissions and functional status at the end of the project.

In a study of 38 hypertensive Canadian steelworkers, Haynes and colleagues examined the effects of an adjunctive educational program.[20] Patients who had neither adhered with previously prescribed medications nor were at goal diastolic blood pressures six months after starting treatment were randomly assigned to an experimental or control group. Members of the experimental group were taught to measure their own blood pressure, asked to chart their blood pressures and pill taking, and taught to adjust their pill taking to their daily habits and rituals. This group was also monitored biweekly, and these patients were praised when improvements in adherence and blood pressures were noted. Six months after the study had begun,

adherence in the experimental group had risen by 21.3% while control group adherence had fallen by 1.5%. Blood pressures fell in 17 of 20 experimental group patients (to goal in 6) and in 10 of 18 control patients (to goal in 2).

Step 5: Evaluate the Plan

Table 5 summarizes the findings related to the fifth step of the educational process. Several investigators have noted the value of eliciting patient feedback throughout the interview.[14,23-25,30,36]

Korsch and associates were the first to report that giving patients an opportunity to ask questions had a positive effect on patient satisfaction and adherence.[23] In 1977, Roter showed the efficacy of eliciting and responding to patient questions.[30] She randomly assigned adult patients in a general medical practice to an educational program that trained them to ask more questions about their problems and therapy during visits with their physician, with the intention of helping patients become better informed. The control group continued to receive care in the traditional manner. A subsequent evaluation showed that patients in the experimental group did indeed take a more active questioning role during their visits, became better informed, and demonstrated improved continuity of care than did patients in the control group.

In her study of physician-patient communication, Svarstad reported that when physicians made an effort to identify patient nonadherence, patients were more apt to admit their difficulties.[36] The physicians who used this information as a basis for advising their patients of alternative ways of coping with undesirable side effects of treatment regimens had increased patient adherence.

Li and co-workers examined the effectiveness of a media program that included—among varied combinations of four interventions—a physician-delivered message to encourage smoking cessation among 1,179 young women in two public family-planning clinics.[25] The physician message included identifying patient barriers to the recommendation to quit smoking and offered suggestions on how to overcome those barriers. A significantly greater number of patients who received this intervention quit smoking than did those who did not have the benefit of the physician message.

In their study of surgical patients, Egbert and colleagues found that providing encouragement, support, and positive reinforcement to patients enhanced the likelihood of patients' cooperating with therapeutic recommendations.[14] Several studies corroborated the findings of Egbert and associates.[19,20,24,25,29]

Close monitoring of patient behavior, facilitated by a careful documentation of interventions in the medical record, is another method of evaluating outcomes that has been shown to have a positive effect on adherence. Levine and Britten reported this in their study of individualized instruction of patients with hemophilia.[24] Careful monitoring enabled physicians to quickly identify and adjust treatment regimens to suit patients' medical conditions and living situations.

TABLE 5.—*Step 5: Evaluating the Plan*

Physician Behavior	*Source**
Provide opportunities for patient to ask questions	10, 18, 19, 23, 24, 29, 30, 31, 33, 34, 35, 36
Explore patient's understanding of plan	19, 22, 24
Explore patient's expected adherence	22, 25, 29, 36
Work with patient to overcome obstacles to adherence	22, 24, 25, 29, 36
Give encouragement, support, reassurance	14, 19, 20, 24, 25, 29
Monitor patient's progress	20, 22, 24, 25, 29, 32, 36
Record plan in medical record	20, 22, 24, 25, 29, 32, 33, 34

*Numbers refer to those in list of references at end of article

Discussion

The physician's role as a patient educator is not new. The word "doctor" comes from the Latin, *docere*, meaning "to teach, to lead forth," and as early as the fifth century BC, Hippocrates endorsed the practice.[43] In 1910 Abraham Flexner, in his highly regarded commissioned report on the state of medical education in the United States, affirmed the view that "the physician's function is fast becoming social and preventive, rather than individual or curative," and urged physicians, "through measures essentially educational, to enforce the conditions that prevent and make positively for physical and moral well-being."[44(p260)] Physicians are once again being encouraged to use educational strategies as a means of enhancing patient decision-making skills.

Currently there appear to be two major educational theories guiding physicians in their role as patient educator. According to Brunton, physicians most frequently use the pedagogic approach in that they assume an authoritative role by determining the nature and scope of the educational process.[37] Often the main focus of this type of educational intervention is to increase the patient's knowledge and understanding of the diagnosis and treatment plan. This concept of patient education, with its emphasis on imparting information and instructions during the concluding segment of the interview, is appropriate and, at times, imperative. Critics of this approach think it is limited in its potential for effecting decision making leading to behavioral change because it is physician-dominant, informational in content, and tends to foster patient passivity and dependence if used exclusively.[7,8,45,46] Another criticism is that when patients are only passively involved in the educational process, their commitment and determination to carry out the recommended treatment regimen may be undermined. While special circumstances necessitate using the pedagogic approach, patients have objected to this method, viewing it as authoritarian and paternalistic.[7,47,48] For some patients, it can lead to resentment, resistance, and, ultimately, to their changing physicians in hopes of finding one who relates to them in a more egalitarian manner.[49,50] The deleterious effects of using the pedagogic approach inappropriately are well chronicled in the adherence literature and include failed rapport, nonadherence, frustrated physicians, and an increased risk of malpractice suits.[2,3,51,52]

This review of the literature offers physicians an alternative approach to their role of patient educator. By using various facilitative behaviors that are initiated at the start of the interview and continued throughout the physician-patient relationship, physicians can encourage and promote the active participation of patients. Because active patient involvement in the decision-making process has been shown to enhance motivation and build commitment to the therapeutic plan, there is reason to think that the systematic use of these physician-initiated behaviors—which are generic and apply to clinicians in all types of settings—can significantly increase patient adherence.

Training physicians in patient education skills is still relatively new, but medical school curricula are reflecting

change as is evidenced by reports of those involved in teaching interviewing skills to students.[53-56] According to the *Directory of Health Education Programs in Medical Education*, there are currently 120 patient education programs in the United States at the medical school or residency level that are involved in teaching these skills to physicians.[56] Physicians in one residency program who were taught to use the ADULT framework in their practices reported more positive attitudes toward patient education and less difficulty conducting patient education activities than physicians in other programs who were not taught these skills.[57-59]

Beyond the narrower issue of adherence, nearly every aspect of medicine relies heavily on educational interventions for success. In the final analysis, each time a physician interacts with a patient, that physician is in a position to determine the educational approach to be used. After reviewing the literature, it is apparent that both the widely practiced pedagogic and the newer andragogic approaches to patient education are clinically relevant. Substantial evidence supports the increased use of the andragogic approach not only because it offers the potential for improving patient adherence, but because it recognizes and treats patients as adults while enhancing their overall physical and mental growth and development.

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Conferences and Reviews

Pathophysiology and Management of Endometrial Hyperplasia and Carcinoma

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An edited summary of an Interdepartmental Conference arranged by the Department of Medicine of the UCLA School of Medicine, Los Angeles. The Director of Conferences is William M. Pardridge, MD, Professor of Medicine.

Endometrial cancer is currently the commonest pelvic malignancy affecting American women, most of whom share the same pathophysiologic basis, that is, unopposed estrogenic stimulation. The initial result of hyperestrogenism is the development of endometrial hyperplasia, which is reversible in most cases by appropriate hormonal therapy. Persistent stimulation eventually leads to atypical hyperplasia with nuclear atypia and invasive carcinoma. Because there is no cost-effective screening method for the detection of endometrial hyperplasia and carcinoma, it is essential to survey the high-risk population with appropriate diagnostic techniques. After diagnosis, therapy should be individualized based on pathologic findings (cell type and histologic grade) and extent of disease (International Federation of Gynaecologists and Obstetricians stage, depth of myometrial invasion, and pelvic and para-aortic lymph node status). Recent studies suggest that sex hormone receptors and nuclear DNA ploidy patterns provide useful prognostic information independent of histologic grade.

(Fu YS, Gambone JC, Berek JS: Pathophysiology and management of endometrial hyperplasia and carcinoma. West J Med 1990 Jul; 153:50-61)

YAO S. FU, MD*: Endometrial cancer is currently the commonest malignant neoplasm of the female genital tract in American women.[1] Its age-adjusted incidence rates remained stable at 23.2 to 24.6 per 100,000 between 1940 and 1970.[2] Beginning in 1970, the incidence of endometrial cancer increased gradually and reached a peak of 30 per 100,000 in the mid-1970s. Since then, a near comparable decline has occurred, most notably among women aged 25 to 64 years.[2] The screening of 2,586 asymptomatic women older than 40 years in early 1980 found the prevalence and incidence rates of endometrial cancer to be 7 and 1.7 per 1,000, respectively.[3] This frequency is comparable with that of squamous carcinoma in situ of the cervix in young women. The endometrial sampling techniques used in this study, however, are thought to be too costly and are unsuited for screening an asymptomatic population.

The five-year survival rates for endometrial cancer reported by the American Cancer Society decreased from 89% to 83% for whites and from 61% to 52% for African-Americans between 1975 to 1976 and 1979 to 1984.[1] This trend may be explained by changes in the etiologic and risk factors during the past two decades. In this conference, we discuss the pathophysiologic basis for the development of endometrial carcinoma, the significance of pathologic findings, and the management of patients with endometrial hyperplasia and carcinoma.

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Risk Factors Associated With Endometrial Cancer

JOSEPH C. GAMBONE, DO†: Various risk factors have been associated with an increased incidence of endometrial cancer in "susceptible" women. These factors should be recognized because most of them can be corrected or controlled; thus decreasing the risk of this lesion in certain patients. Many patients in whom adenocarcinoma of the endometrium develops, however, will not have these risk factors identified. Conversely, in patients who may seem to be at risk, the lesion may never develop. The common characteristic or underlying condition in these risk factors is "unopposed estrogen." These risk factors include exogenous estrogen therapy, the polycystic ovary syndrome and functioning ovarian neoplasms, late menopause, infertility, and obesity. Pelvic irradiation is also a known risk factor for adenocarcinoma of the endometrium. Two other risk factors, hypertension and diabetes mellitus, are now thought to be a consequence of obesity and not causally related to endometrial cancer.

It has been known since 1957 that giving diethylstilbestrol to rabbits could produce metastasizing endometrial cancer.[4] In addition to studies in animals, several lines of evidence strongly support the concept that unopposed estrogen is associated with an increased risk of endometrial cancer. For example, patients with granulosa-theca cell tumors of the ovary have a high incidence of endometrial carcinoma.[5,6] These ovarian tumors, although uncommon, are capable of high estrogen production. The risk for adeno-

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carcinoma of the endometrium in these patients is increased, especially if the patient is postmenopausal. Other nonfunctional ovarian tumors, and even hyperplasia of ovarian stroma, have been associated with endometrial cancer.[7] The fact that postmenopausal patients are at the highest risk emphasizes that the absence of progesterone opposition on the endometrium is a primary factor because these women have lower levels of estradiol and estrone than do premenopausal women. Premenopausal women who are ovulatory, even though they have considerably more estrogen, also have the protective effect of progesterone.

By far the most publicized and controversial risk factor for endometrial cancer is exogenous estrogen use.[8] The use of unopposed exogenous estrogen is associated mostly with malignant disorders that have a favorable prognosis. Many studies have shown that most, but not all, endometrial cancers that occur in patients receiving estrogen are low stage and well differentiated with excellent survival rates.[9,10] An early "version" of the oral contraceptive, the sequential pill, was withdrawn from the market when its association with adenocarcinoma of the endometrium became evident. In this contraceptive preparation, high levels of synthetic estrogen alone for most of the cycle were opposed by progesterone for only a short interval (usually only five days). The combination contraceptive pill with progestin given with each pill daily has the opposite effect, with a lower incidence of endometrial cancer than in nonusers, thus providing a protective effect.[11]

Endometrial cancer is predominantly a disease of postmenopausal women, with only about 5% of cases occurring in women younger than 40.[7,12] Chronic anovulation with long periods of unopposed estrogen, as occurs in patients with the polycystic ovary disease, is a common finding in premenopausal patients in whom endometrial cancer develops at an early age.[12]

When estrogen is given as hormonal therapy for postmenopausal women who have not had a hysterectomy, a progestin should be prescribed to oppose the estrogenic effect on the endometrium.[13] Premenopausal women with chronic anovulation and chronically elevated estrogen levels should receive pharmacologic replacement of progestins to oppose this estrogenic effect, or, if pregnancy is desired, ovulation should be induced.

The average (median) age of menopause in the United States is 51.4 years. Women whose menopause occurs past age 52 have an increased risk of endometrial cancer. A longer period of chronic anovulation and unopposed estrogen in these women is considered to be the predisposing factor.

Infertility is associated with a higher incidence of endometrial cancer. Even women who have only one child are at greater risk than multiparous women. The ovulatory dysfunction (less progesterone) in some cases of infertility and the lack of some protective effect that multiple term pregnancies may provide have been suggested to explain this risk factor.

Obesity is perhaps the most studied risk factor for endometrial cancer. The hypothesis that endogenous estrogen metabolism plays a role in the pathogenesis of endometrial cancer in postmenopausal women is based on the finding that obese older women have enhanced endogenous estrone and estradiol production[14,15] and are at greater risk for this tumor developing.[16]

Obese women have decreased levels of sex hormone-binding globulin, a protein that binds to estradiol[17]; as the levels decrease, more estradiol is available to tissues. This dual effect of body size on estradiol is depicted in Figure 1.[18] According to this hypothesis, obese women have higher total levels of estrogen and proportionately greater bioavailable fractions than do slender women.[18] Thus, postmenopausal women who are obese, particularly if they are nulliparous, are at greater risk for the development of endometrial hyperplasia and endometrial cancer. The association of hypertension and diabetes directly with endometrial cancer is questionable because obesity itself has a strong association with these two medical disorders.

Finally, previous pelvic irradiation administered for various other pelvic tumors is associated with an increased incidence of endometrial carcinoma. This may be due to the irradiation, to the underlying cause for which the irradiation was given, or a combination of both.

Significance of Pathologic Findings in Endometrial Hyperplasia and Carcinoma

Dr Fu: From Dr Gambone's review, it is apparent that most endometrial cancers develop because of hyperestrogenism. A few women in whom endometrial cancer develops, however, have no signs of hyperestrogenism. Comparing the two groups has shown some interesting differences. In the group with an excess of endogenous or exogenous estrogen, endometrial carcinoma is associated with endometrial hyperplasia and is usually well or moderately differentiated, superficial in myometrial invasion, and prognostically favorable. In the other group, carcinoma develops in a background of normal or atrophic endometrium and is poorly differentiated and more aggressive.[19,20] A recent decrease in the survival of patients with endometrial cancer can be attributed to a decline in the incidence of prognostically favorable cancer seen during the 1970s.

Histologic Classification of Endometrial Hyperplasia

Previous retrospective and back-dated prospective studies have consistently shown that endometrial hyperplasia often precedes, or coexists with, carcinoma. Histologically, endometrial hyperplasia is divided into cystic, adenomatous, and atypical adenomatous types with increasing architectural complexity. In our review of 96 women with endometrial hyperplasia who were observed from 1 to 13 years, the architectural patterns correlate with the likelihood of regression and persistence. Of the women with cystic hyperplasia, 55% had a return to normal, as compared with 31% of those with adenomatous hyperplasia.[21] In postmenopausal women receiving estrogen therapy, the increment of estrogen dose correlates with increasing complexity of the architectural pattern.

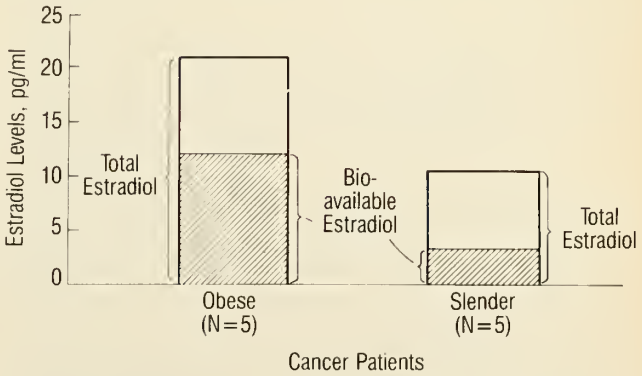

Figure 1.—Using a bioassay for tissue extraction of estradiol, serum from obese women was found to have higher total estradiol levels and also a greater fraction that is available to tissue (from Gambone et al[18]; reproduced with permission from *The American College of Obstetricians and Gynecologists*).

The risk of progression from hyperplasia to carcinoma is similar for both cystic and adenomatous hyperplasias (9%). The nuclear atypia is a more reliable indicator of progression. The progession rate is 3% for hyperplasia without atypia, 6% hyperplasia with mild atypia, and 20% hyperplasia with moderate atypia.[21] In the study by Kurman and associates, 23% and 1.6% of endometrial hyperplasias with and without nuclear atypia, respectively, progressed to invasive carcinoma.[22] Thus, the pathologic assessment of endometrial hyperplasia should indicate both the architectural and nuclear abnormalities.

Methods of Diagnosis

Endometrial hyperplasia and cancer may be detected by the use of appropriate cellular specimens interpreted by skilled observers. Cervical smears, which depend on the exfoliation of abnormal endometrial cells, have an accuracy of less than 50% to 75% for detecting carcinoma.[23-25] These specimens have consistently failed to detect endometrial hyperplasia and well-differentiated carcinoma because these lesions do not shed an adequate number of representative cells for diagnosis. In addition, to interpret these cells accurately, considerable experience and skill are needed.[23-25]

Various office procedures for direct endometrial sampling have been tested and evaluated, such as endometrial aspiration, endometrial brushing, endometrial biopsy, and vacuum curettage. Their accuracies for detecting endometrial carcinoma range from 74% to 97% but only 32% to 80% for hyperplasia.[26-30] In many institutions, endometrial curettage is still the traditional method for detecting endometrial hyperplasia and cancer. The cell type and histologic grade of endometrial carcinoma are established on the basis of histologic specimens.

Types of Endometrial Cancer

Most primary endometrial cancers are adenocarcinoma and its variants with additional metaplastic cells. Squamous and small cell carcinomas rarely occur in the endometrium; some of the latter may express neuroendocrine differentiation. In two large series, 60% to 65% of endometrial cancers were classified as adenocarcinoma, 19% to 22% as adenoacanthoma (Figure 2), 7% to 14% adenosquamous carcinoma, 1% to 6% clear cell carcinoma, 1% secretory adenocarcinoma, and 5% papillary serous carcinoma.[31,32] Adenoacanthoma refers to adenocarcinoma coexisting with cytologically benign squamous epithelium, whereas adenosquamous carcinoma contains adenocarcinoma and cytologically malignant and locally infiltrative squamous carcinoma.

Clear cell carcinoma consists of polygonal, hobnail-shaped, or flattened cells. An accumulation of abundant glycogen in cytoplasm results in the clear appearance. Clear cell carcinoma generally occurs in older women with a mean age of 67 years.[33] In secretory carcinoma, the neoplastic cells simulate normal early secretory endometrial cells with perinuclear vacuoles. Uterine papillary serous tumor resembles ovarian papillary serous carcinoma and has a predominantly papillary growth pattern and markedly atypical epithelial cells with nuclear anaplasia, macronucleoli, and high mitotic activity.[34]

The histologic classification based on cell type provides important prognostic information. Usual endometrial adenocarcinoma, adenoacanthoma, and secretory carcinoma have similarly favorable prognoses, whereas a poor prognostic group includes adenosquamous carcinoma, papillary serous carcinoma, and clear cell carcinoma. The reported five-year survival rates in two large series were 72% to 75% for adenocarcinoma, 68% to 87% for adenoacanthoma, 26% to 48% for adenosquamous carcinoma, 35% for clear cell carcinoma, and 51% for papillary carcinoma.[31,32]

Histologic Grade

The histologic grade of endometrial cancer indicates the degree of differentiation in the glandular elements. The morphologic criteria have been variable. The method of the International Federation of Gynaecologists and Obstetricians (FIGO) is based on the proportion of glandular and solid elements into three grades.[35] Well-differentiated (grade 1) carcinomas consist of 98% or more glandular or papillary formations, moderately differentiated carcinomas (grade 2) contain 2% to 50% of solid areas, and poorly differentiated or undifferentiated carcinomas (grade 3) are more than 50% or entirely solid in pattern. The Gynecologic Oncologic Group has modified the FIGO scheme by increasing the solid foci up to 5% for grade 1 and 5% to 50% for grade 2 tumors. The World Health Organization[36(pp64-65)] and others[31,32] combine both architectural and cytologic features, including mitotic activity and nuclear and nucleolar findings, for final grading; others prefer grading by nuclear structure alone.[32,37]

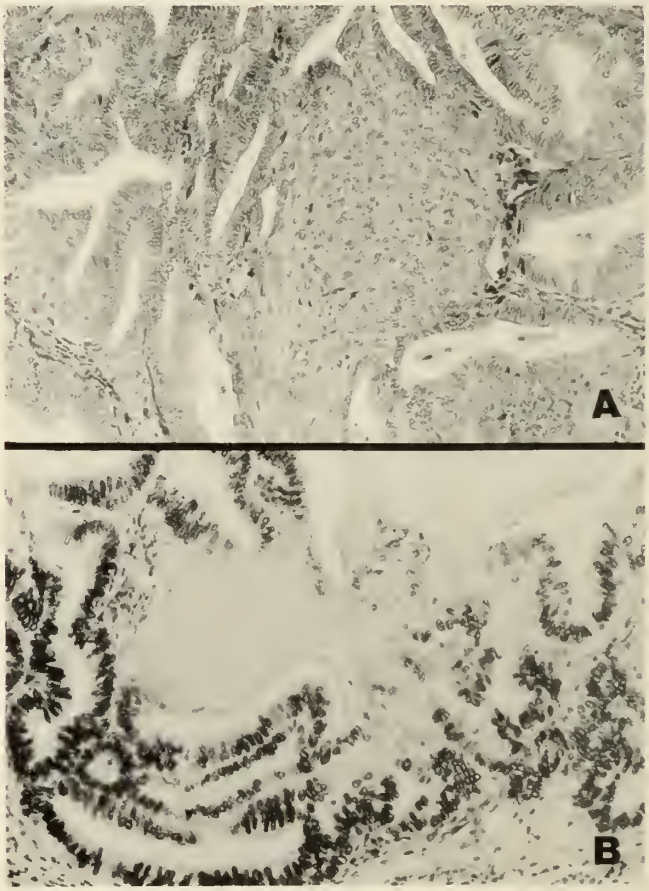

Figure 2.—**A,** Adenoacanthoma of endometrium consists of two cellular elements: a well-differentiated adenocarcinoma consisting of irregular, back-to-back glands and solid nests of metaplastic, cytologically benign squamous cells (center) (hematoxylin and eosin; original magnification × 250). **B,** A formalin-fixed, paraffin section of the similar area is stained immunohistochemically for estrogen-receptor proteins using monoclonal antibody ER-CIA (Abbott Laboratories, North Chicago, Ill). An intense nuclear staining is seen in more than 95% of glandular cells, indicating the presence of estrogen-receptor proteins. Squamous cells, on the other hand, are nonreactive (counterstained by methyl green; original magnification × 250).

Despite the differences in criteria, the histologic grade of the neoplasm correlates with the depth of myometrial invasion, pelvic and para-aortic lymph node status, and survival. The consistency and the reproducibility among the pathologists, however, have remained a problem.

Spread of Endometrial Cancer

Endometrial cancers spread by direct invasion of the myometrium and uterine cervix, vascular lymphatic dissemination, and transtubal passage to the peritoneal cavity. The extent of disease can be further defined on the basis of uterine specimens and the sampling of pelvic and para-aortic lymph nodes. With increasing depth of myometrial invasion, the risk of local and distant spreads by vascular lymphatic channels is enhanced. Pelvic and para-aortic lymph node involvement, reflecting an advanced stage of disease, has been correlated with poor differentiation and deep myometrial invasion. Intraoperative consultation for assessing the histologic grade and the depth of myometrial invasion in a removed uterus is recommended for determining the need for obtaining specimens of pelvic and para-aortic lymph nodes. Pelvic washings for cytologic examination are important for determining the pelvic extension and prognosis. In one study, 29% of women with positive peritoneal cytologic findings had tumor recurrence after a hysterectomy, as compared with 3% with normal cytologic findings.[38]

Recent Developments

Recent technical improvements have made it possible to determine steroid hormone receptors and nuclear DNA ploidy patterns of endometrial carcinoma in paraffin-embedded tissue. These analyses offer an objective and more accurate assessment of malignancy than histologic grade.

The DNA ploidy analysis can be determined by a flow cytometer or digital imaging system.[39] Single cells are extracted from fresh or paraffin-embedded tissue, stained with specific dye for DNA, and measured under visible or ultraviolet light. Diploid tumors have the same range of DNA content as that of normal control cells. Aneuploid neoplasms present separate peak(s) deviated from the normal diploid peak.[40] The DNA ploidy analysis identifies a subset of aneuploid, more aggressive tumors within the same histologic grade. For example, 10% of grade 1, 31% of grade 2, and 78% of grade 3 tumors have aneuploid patterns.[40] Patients with aneuploid tumors have lower survival and higher tumor recurrence rates than those with diploid tumors.[40] The mortality was 11% (4/38) for women with diploid tumor but 50% (7/14) for those with aneuploid tumor. Among the patients who died, the lengths of median survival were 27.5 and 17 months for the diploid and aneuploid groups, respectively.[40] The sum of S (synthesis phase) and grade 2 cells determined by flow cytometry, which corresponds to the proliferative activity of tumor, offers additional prognostic information. A low proliferative fraction is associated with a favorable outcome.[41]

Unoccupied estrogen and progesterone receptor proteins have been assayed in cytosol preparations from normal, hyperplastic, and carcinomatous endometria.[42] In normal endometrium, estrogen receptors reach a peak before ovulation and decline progressively after ovulation to low levels before menstrual bleeding. Progesterone is thought to reduce the levels of estrogen and progesterone receptors.[43] This finding may provide an explanation for the antiproliferative effect of progestins in normal and abnormal endometrium.

By biochemical assay, the estrogen receptor content in atrophic and hyperplastic endometrium is similar to that of proliferative endometrium.[42] In atypical adenomatous hyperplasia with increasing architectural complexity and nuclear atypia, there is a loss of estrogen receptors in some of the cells. In endometrial carcinomas, only two thirds are positive for estrogen receptors, and their levels are comparable with, or lower than, those in proliferative endometrium.[44] Most authors have found that well- and moderately differentiated tumors are more likely to be positive and to have a higher level of estrogen and progesterone receptors than poorly differentiated neoplasms.[44-47] Adenocarcinomas have a higher estrogen receptor content than adenosquamous carcinoma (mean 65.1 versus 29.0 fmol per mg of protein).[45] Although estrogen receptors tend to reduce with increasing clinical stage, there is no correlation between the receptor and the depth of myometrial invasion.

The prognostic value of receptor assays was shown by Geisinger and colleagues, who found prolonged survival among women whose tumor contained estrogen receptors, progesterone receptors, or both, greater than 10 fmol per mg of protein.[41] By multivariate analysis, the estrogen and progesterone receptor status is a more reliable predictor of survival than histologic grade.[44] This is confirmed by Chambers[45]; in his study, the optimal cutoff for the survivor and nonsurvivor groups is 20 fmol per mg of protein for estrogen receptors and 7 fmol per mg of protein for progesterone receptors. Progesterone receptor positivity also correlates with a clinical response to progestin therapy in 92% of cases.[44]

The biochemical assay of endometrial tissue for estrogen and progesterone receptors has several limitations, such as the need for fresh tissue specimens. Including normal endometrium and myometrium can lead to false-positive results. An inadequate amount of tumor tissue for assay and a heterogeneous distribution of estrogen receptors in tumor tissue are sources of false-negative tests.[48]

With the use of monoclonal antiestrophilin antibodies[49] and immunohistochemistry, estrogen receptor-positive cells can be visualized on frozen or paraffin sections (Figure 2).[50-52] This minimizes the sampling problems already mentioned above and is suitable for both retrospective and prospective studies.[51,52] By immunohistochemistry, 92% (34/37) of grade 1, 62% (23/37) of grade 2, and 12% (3/26) of grade 3 cancers were estrogen receptor-positive.[51] The agreement between biochemical and immunohistochemical assays is in the range of 92%.[51]

In summary, determinations for estrogen and progesterone receptors and DNA ploidy patterns can improve the prognostic accuracy achieved by routine histologic examination. They may prove to be useful in selecting therapeutic methods.

Management of Endometrial Hyperplasia and Carcinoma (Modified With Permission From Berek and Co-workers[53])

Endometrial Hyperplasia

JONATHAN S. BEREK, MD*: The treatment of endometrial hyperplasia should be individualized because the results of independent studies suggest that most endometrial hyperplasias do not progress to invasive cancer.[21,22] Hysterectomy is not necessary to treat most of these lesions.

Progestin therapy is appropriate for most patients with endometrial hyperplasia without atypia. A regimen of medroxyprogesterone acetate, 5 to 10 mg given either 10 to 12 days per month, or daily, each for about 3 months, will

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convert 75% to 90% of the hyperplasia without atypia to a normal endometrium. A similar trial may be used in patients whose lesions possess considerable cytologic atypia, although daily treatment is recommended for about three months followed by another biopsy of the endometrium. If hyperplasia persists, either a hysterectomy can be done, or if there is a contraindication, high doses of a progestin, for example, 80 to 200 mg per day of medroxyprogesterone, can be administered for two to three months to obviate hysterectomy in those patients.[53]

Clinical Presentation of Endometrial Cancer

Most patients (90%) with endometrial carcinoma present with abnormal vaginal bleeding, usually postmenopausal bleeding. Conversely, most women (greater than 80%) who present with postmenopausal bleeding do not have endometrial cancer; most bleeding in these patients is caused by a benign condition, such as atrophic vaginitis or a vaginal infection. In perimenopausal or anovulatory premenopausal women, heavy and prolonged vaginal bleeding may be a sign of malignancy. In thin, elderly, estrogen-deficient women, vaginal bleeding may not be present because of cervical stenosis, which can produce a hematometra, or a purulent collection, a pyometra.

Most patients with endometrial cancer are obese postmenopausal women, although a third are not obese and have no sign of hyperestrogenism.[19] On pelvic examination, the cervix and vagina should be inspected and palpated to exclude metastases and other causes of abnormal vaginal bleeding. The uterus is often only slightly enlarged, although it may be large due to a hematometra or pyometra. A rectovaginal examination should be done to evaluate the adnexal structures and the rectum. Although the results of an abdominal examination are normal in most patients, ascites may be present; in advanced cases, hepatic or omental metastases may be palpable in the upper abdomen.

All patients suspected of having endometrial carcinoma should have an endometrial biopsy and an endocervical curettage. When an endometrial biopsy is done in the office and it definitely documents cancer, treatment can be planned without an examination under anesthesia. Because there is a false-negative rate of about 10%, normal findings on office endometrial biopsy in symptomatic patients cannot be considered definitive, and these patients should therefore have a fractional curettage under anesthesia. Furthermore, a diagnosis of endometrial hyperplasia on office endometrial biopsy also requires a fractional curettage.[54]

When dilatation and curettage are done under regional or general anesthesia, the endocervical canal is curetted before cervical dilatation and the tissue placed in a separate container. The uterus is then sounded and the cervix dilated. The endometrium is systematically curetted and the tissue specimen placed in another separate container so that tissues taken from the endocervix and endometrium can be evaluated separately.

Before any planned surgical procedure, routine blood work should be done, but extensive noninvasive and radiographic tests are not warranted. Cystoscopy and sigmoidoscopy are necessary only if bladder or rectal involvement is suspected clinically.[55] A barium enema should be done in patients who have occult blood in the stool or who have a recent change of bowel habits because in rare cases a coexistent colon cancer can occur.[55,56] A pelvic and abdominal computed tomographic scan may be helpful to document metastatic disease when the patient has abnormal results on liver function tests, clinical hepatomegaly, a palpable upper abdominal mass, palpable extrauterine pelvic disease, or clinical ascites.[54]

Hysteroscopy has been used to determine the extent of disease,[57-59] and when there is diffuse disease in the endometrial cavity, two thirds of patients have myometrial invasion deeper than the inner third.[59] The depth of myometrial invasion can be shown with magnetic resonance scanning, and, therefore, this might prove useful to determine the presence of disease beyond the inner third of the myometrium.[60] Patients with such tumor invasion may benefit from appropriate surgical staging, and preoperative identification might permit a referral when surgical staging is unavailable.

Staging of Endometrial Cancer

The former clinical staging system used for endometrial carcinoma is that of the International Federation of Gynaecologists and Obstetricians (Table 1). The old staging is clinical and is based on the physical examination and preoperative investigations. At exploratory laparotomy, however, the cancer may be found to be more or less advanced than was apparent clinically. Using this clinical system, understaging occurs in about 10% of patients with stage I disease.

The new FIGO staging system (1988) (Table 2) uses a surgical stage that will determine the subsequent management and predict the prognosis. The older, clinical FIGO stage could not be changed on the basis of the operative findings.[61-65] The advantage of the new surgical staging system is that it documents with greater accuracy the actual extent of disease.

A diagnosis of stage II disease now recognizes that the cancer and normal endocervical tissues are contiguous, based on the evaluation of the uterine specimen. When the tumor tissue in the prehysterectomy endocervical curettage is completely separate from the endocervical tissue, often representing contamination from the corpus, the prognosis is the same as for patients with stage I disease.[66,67] The false-positive rates for prehysterectomy endocervical curettage are 40% to 50%, whereas false-negative rates are low, less than 2%.[66,67] Thus, the surgical confirmation (by hysterectomy) of true cervical involvement is much more

TABLE 1.—*Staging for Endometrial Carcinoma (Former Clinical Staging System) of the International Federation of Gynaecology and Obstetrics*

Stage	*Extent of Carcinoma*
0	Carcinoma in situ
I	Confined to corpus
IA	Length of the uterine cavity is 8 cm or less
IB	Length of the uterine cavity is more than 8 cm
Stage I cases subgrouped by histologic grade	
Grade 1	Highly differentiated adenomatous carcinoma
Grade 2	Moderately differentiated adenomatous carcinoma with partly solid areas
Grade 3	Predominantly solid or entirely undifferentiated carcinoma
II	Carcinoma has involved the corpus and cervix but no extension outside the uterus
III	Carcinoma extends outside the uterus but not outside the true pelvis
IV	Carcinoma extends outside the true pelvis or has obviously involved the mucosa of the bladder or rectum; bullous edema as such does not permit allocating to stage IV
IVA	Spread of growth to adjacent organs
IVB	Spread to distant organs

valid. Although any actual cervical extension documents stage II disease, it is useful to distinguish clinically between gross cervical involvement, which can be detected on physical examination, and microscopic cervical involvement, where the cervix is clinically normal and the extension is based only on microscopic cervical disease. Microscopic cervical involvement has often been unofficially designated stage II "occult" endometrial carcinoma.[54] Stage I and stage II occult disease can be managed in the same manner, as will be discussed.

Most endometrial carcinomas are diagnosed while the disease has not spread beyond the uterine corpus. The distribution of endometrial carcinomas by the former clinical stage at initial presentation is shown in Table 3.[68]

Treatment of Endometrial Cancer

The principal treatment of endometrial cancer is an exploratory laparotomy, total abdominal hysterectomy, and bilateral salpingo-oophorectomy. This operation, whenever feasible, should be done for all patients. Adjuvant irradiation to prevent vaginal recurrence and to treat lymph node metastases should be selectively administered to patients based on the operative findings.

The role of irradiation in the management of endometrial cancer is controversial because few controlled studies have been undertaken and existing studies are not controlled for potential differences in prognostic variables. Therefore, the actual influence of radiation therapy on survival is difficult to prove. Recent data on surgical staging, however, have permitted a better understanding of the prognostic variables for the disease, which has led to a more individualized approach to adjuvant irradiation.

The maximum amount of prognostic information is obtained through surgical staging, and, therefore, the trend is toward the selective application of postoperative rather than preoperative irradiation. Preoperative brachytherapy for patients with poorly differentiated tumors is recommended by some investigators.[69]

Stage I and stage II occult disease. The initial approach for patients with stage I and presumed microscopic stage II (occult) endometrial cancer is exploratory laparotomy, abdominal hysterectomy, and bilateral salpingo-oophorectomy. Removal of a vaginal cuff is unnecessary, but the adnexa should be excised because they may be the site of microscopic disease or separate, synchronous primary ovarian cancers.[70-73] Surgical staging should be done in those patients with poorly differentiated lesions and those with histologic features signaling a poor prognosis—for example, adenosquamous or papillary serous carcinomas.[54]

The staging laparotomy should include a thorough inspection of all intra-abdominal contents.[54,74] Peritoneal washings should be taken from the pelvis, the paracolic gutters, and subdiaphragmatic areas using 50 ml of a normal saline solution instilled into each area and submitted for cytologic evaluation. A biopsy should be done of any adhesions or suspicious lesions on the peritoneum. When hysterectomy and bilateral salpingo-oophorectomy are done, the retroperitoneal spaces should be entered bilaterally so that the pelvic and para-aortic lymph nodes can be inspected, palpated, and enlarged lymph nodes removed. The uterus should be opened while the patient is anesthetized. Surgical staging should be done on patients whose specimens have substantial myometrial invasion—that is, the outer half to two thirds of the uterine thickness—or cervical extension. The para-aortic lymph nodes at the level of the bifurcation of the aorta are resected. If enlarged lymph nodes are visible or palpable, they should be submitted for frozen section.

The rates of pelvic and para-aortic lymph node metastases by histologic grade and by myometrial invasion are presented in Tables 4 and 5, respectively.[65,75] The rate of distant metastases relative to grade and myometrial invasion is presented in Table 6.[77]

In selected obese patients and those who have serious

TABLE 2.—*Carpus Cancer Staging (1988) (Revised Surgical Staging) af the Internatianal Federatian af Gynaecalagy and Obstetrics**

Stoge	*Extent of Corcinomo*
IA	Tumor limited to endometrium
IB	Invasion to ≤ half myometrium
IC	Invasion > half myometrium
IIA	Endocervical glandular involvement only
IIB	Cervical stromal invasion
IIIA	Tumor invades serosa or adnexa, or both, or positive peritoneal cytology, or both
IIIB	Vaginal metastases
IIIC	Metastases to pelvic or para-aortic lymph nodes or both
IVA	Tumor invades bladder or bowel mucosa or both
IVB	Distant metastases including intra-abdominal or inguinal lymph node or both

*In addition, all lesions should be graded as either grade 1 (well differentiated), grade 2 (moderately differentiated), or grade 3 (poorly differentiated).

TABLE 3.—*Distributian by Stage af Carcinama af the Endametrium**

	Potients	
Stoge	*Number*	*Percent*
I	8,550	74.3
II	1,690	14.7
III	822	7.2
IV	314	2.7
No stage	125	1.1
Total	11,501	100.0

*From the International Federation of Gynaecology and Obstetrics.[68]

TABLE 4.—*Pelvic and Para-aartic Nadal Metastases Versus Histalagic Grade af Stage I Endametrial Carcinama**

Histologic Grade	*Pelvic Nodes*			*Aortic Nodes*		
	Number	*Positive*	*%*	*Number*	*Positive*	*%*
1	290	9	3.1	267	5	1.9
2	302	34	11.3	268	20	7.5
3	158	32	24.7	150	24	16.0
Total	750	82	10.9	685	49	7.2

*Combined Gynecologic Oncologic Group data from Boronow et al[65] and Morrow et al.[75] Of 528 patients reported by Morrow et al, 73 had stage II occult disease.

TABLE 5.—*Pelvic and Para-aartic Nadal Metastases Versus Myametrial Invasian af Stage I Endametrial Carcinama**

Myometriol Invasion	*Pelvic Nodes*			*Aortic Nodes*		
	Number	*Positive*	*%*	*Number*	*Positive*	*%*
None	199	4	2.0	175	2	1.1
Inner third	291	15	5.2	265	8	3.0
Middle third	106	14	13.2	98	7	7.1
Outer third	154	49	31.8	147	32	21.8
Total	750	82	10.9	685	49	7.2

*Combined Gynecologic Oncologic Group data from Boronow et al[65] and Morrow et al.[75] Of 528 patients reported by Morrow et al, 73 had stage II occult disease.

medical problems that place them at high risk for an abdominal surgical procedure, a vaginal hysterectomy can be considered. A 94% survival has been reported among 56 patients with stage I endometrial carcinoma who underwent vaginal hysterectomy.[77] Most of these patients had low-grade lesions, and more than half received adjuvant irradiation. This approach is superior to treating these patients with irradiation alone.

Adjuvant irradiation. Adjuvant irradiation has been frequently used to treat patients with low-stage endometrial cancer; a clear improvement in survival, however, has not been documented.[78] Because irradiation for selected high-risk patients significantly decreases the incidence of pelvic and vaginal recurrences, it probably influences survival in this subset of patients. Vaginal recurrences have been shown to be decreased by external or intracavitary irradiation,[64,79] whereas pelvic recurrences may be decreased by external irradiation.[80-82] Although 5,000 cGy is necessary to eradicate microscopic lymph node metastases, grossly enlarged nodes are not effectively treated with this dose of adjuvant pelvic irradiation; they should be surgically resected before administering the radiation.

Before routine surgical staging of endometrial carcinoma became the standard approach, preoperative intracavitary or external irradiation was given because of the concern that vaginal implantation or systemic dissemination would occur as a result of uterine manipulation. Vaginal recurrences in patients with no residual disease in the operative specimen have been reported in 6.2% of patients receiving preoperative intrauterine irradiation, however, eliminating the risk of implantation as a rationale for preoperative irradiation.[83] Primary surgical treatment must be associated with a minimal risk of tumor spread because there is no difference in the rate of distant metastases in patients treated with preoperative versus postoperative pelvic irradiation.[84]

Although the issue of preoperative versus postoperative irradiation is not settled, the ability to individualize the extent and field of postoperative irradiation makes it more practical. The options for postoperative irradiation are vaginal irradiation, external pelvic irradiation, extended para-aortic irradiation, whole abdominal irradiation, and intraperitoneal administration of phosphate P 32.

Vaginal recurrence has a poor prognosis. Vaginal irradiation substantially reduces the incidence of vault recurrence—that is, preoperative or postoperative vaginal brachytherapy has been shown to decrease the incidence of vaginal recurrence from 14% to 1.7%.[64] Vaginal colpostats alone are usually used to deliver a surface dose of 5,500 to 6,000 cGy. Although the morbidity is low, vaginal stenosis can develop in postmenopausal patients who are not having regular vaginal intercourse.

TABLE 6.—*Distant Metastases Versus Histologic Grade and Myometrial Invasion of Stage I Endometrial Carcinoma**

Variable	Patients		
	Number	Metastases	Percent
Histologic Grade			
1	93	2	2.2
2	88	9	10.2
3	41	16	39.0
Myometrial Invasion			
None	92	4	4.3
Inner third	80	8	10.0
Middle third	17	2	11.8
Outer third	33	13	39.4

*From DiSaia et al.[76]

Patients who have grade 1 lesions with minimal invasion (no more than the inner third of the myometrium) have an excellent prognosis with surgical excision alone, and no adjuvant irradiation is necessary. The five-year survival for patients with stage I grade 1 lesions treated surgically only is 96%.[85]

For patients with poorly differentiated carcinomas, those with myometrial invasion greater than a third, those with cervical involvement, and those with pelvic metastasis outside the uterus, external pelvic irradiation significantly decreases the risk of pelvic recurrence.[85] A few patients (1% to 2%) have late complications develop after receiving only postoperative external irradiation.[86]

External irradiation and vaginal brachytherapy are equally effective for controlling microscopic vaginal metastases. Therefore, it is unnecessary to use external and internal irradiation because the morbidity will be excessive. Serious complication rates of 10% to 15% are reported in patients treated with both external and intracavitary irradiation.[73]

Para-aortic irradiation for patients with surgically confirmed para-aortic spread alone, or pelvic and para-aortic spread, has been shown to result in five-year survival rates of 47% and 43%, respectively.[74,87] Para-aortic irradiation is limited to 4,500 to 5,000 cGy because of the potential for damage to the small bowel and spinal cord. Severe enteric morbidity is seen in 2% of patients.[87] Because endometrial cancer may spread in some patients directly to the para-aortic lymph nodes and bypass the pelvic nodes, extended-field para-aortic irradiation may have important use in this cancer. Exploratory laparotomy is now part of the standard procedure for endometrial cancer; biopsy of the para-aortic nodes should therefore be done more routinely, thus documenting more accurately the para-aortic nodal status.

Whole abdominal irradiation for the treatment of patients with either positive peritoneal washings or adnexal or peritoneal metastases is controversial.[88,89] In one series, patients who had positive peritoneal washings or adnexal metastasis received whole abdominal irradiation and had a five-year relapse-free rate of 90%.[55] Patients with visible peritoneal metastases, however, had a five-year relapse-free rate of 0%.[85] Whole abdominal irradiation has been recommended for patients with upper abdominal, peritoneal, or omental metastases that have been completely excised, but there are insufficient data to document its use in these circumstances. In patients with gross residual disease, whole abdominal therapy is not appropriate.

Intraperitoneal instillation of ^{32}P has been used in patients with malignant peritoneal washings, but these patients are also at risk for vaginal and pelvic side-wall recurrences; they should therefore receive external pelvic irradiation. When these treatments were combined, patients treated with external irradiation had excessive chronic intestinal morbidity develop and needed surgical intervention in about 30% of cases.[90] Also, ^{32}P can distribute unevenly in the peritoneal cavity, producing bowel injury from "hot spots." Because the prognostic significance of positive peritoneal washings and the value of ^{32}P must be determined, the treatment of patients with positive cytologic studies with ^{32}P should be done on a research protocol.

The value of adjuvant progestin therapy in early-stage endometrial carcinoma is unknown. One large adjuvant trial in which low-risk stage I patients received either adjuvant medroxyprogesterone (Depo-Provera) or placebo showed no significant differences in five-year survival be-

tween the two groups.[91] Another study treated low-risk stage IA and IB patients with adjuvant progestin therapy and also reported no benefit.[92] Several investigators have advocated the use of prophylactic progestational agents in high-risk patients[92-94]—that is, those with more poorly differentiated lesions or positive findings on peritoneal cytology. Two adjuvant trials currently under way include only patients at high risk for recurrence, and, thus far, the results of both studies suggest some benefit.

Stage II. The new FIGO staging system requires that the endometrial cancer that arises in the uterus extend directly to either the uterine cervical glands (stage IIA) or the cervical stroma (stage IIB), so-called uterine corpus et colli cancer. These findings are documented in the uterine specimen. Preoperatively, when the cervix and endometrium seem to be involved clinically with adenocarcinoma, it may be difficult to differentiate between stage IB adenocarcinoma of the cervix and stage II endometrial carcinoma. The histopathologic examination may not help, and the diagnosis must be made primarily on the basis of clinical features. Postmenopausal women who are obese or who have a bulky uterus are most likely to have endometrial cancer, whereas premenopausal women with a bulky cervix and normal corpus most likely have a primary endocervical cancer.

The optimal therapy for patients with stage II endometrial cancer has not been documented by randomized, prospective studies. An incidence of positive pelvic nodes has been documented in 36% of patients with stage II disease; these nodes, therefore, need to be treated.[93] To control the central pelvic disease, the uterus must be removed in all patients.[92,93] The two main treatment options for patients with stage II disease are either primary surgical excision with a radical hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy; or combined irradiation and surgical therapy—that is, preoperative external pelvic irradiation and intracavitary cesium, followed in six weeks by an extrafascial abdominal hysterectomy and bilateral salpingo-oophorectomy. The results of these two approaches seem to be the same, and the choice of therapy in stage II patients should be individualized.[94]

Surgical-pathologic information can be gained from a radical surgical procedure, but many of these patients are obese, or elderly, with medical problems and are not suitable candidates for extensive surgical intervention. Radical hysterectomy should be used to treat relatively young and healthy premenopausal patients or those with anatomic or other problems that make the use of irradiation more problematic.[94]

The commonest treatment is the use of both radiation and surgical therapy.[95-102] After external pelvic irradiation, or intracavitary irradiation, an extrafascial hysterectomy is done about four to six weeks later to permit the inflammation and edema to subside. Irradiation is used to deliver the maximum radiation dose to the endocervix. In one study of 25 patients treated with external irradiation and a single intracavitary dose of radium, there were no vaginal recurrences and all pelvic recurrences were associated with distant metastases.[101] Also, a radical hysterectomy after the external irradiation does not improve the survival compared with those treated with intracavitary radium and extrafascial hysterectomy. Intestinal morbidity is a substantial problem in patients treated with a combination of radiation and surgical therapy. Serious morbidity has been documented in 5% to 10% of patients treated in this manner.[102]

Complications include small or large bowel obstructions needing surgical intervention and the development of rectovaginal and lower urinary tract fistulas. Irradiation alone has been used in patients with medical contraindications to surgical therapy, in patients with superficial myometrial invasion, and in those with well-differentiated lesions; the outcome is favorable in most patients.[86]

Metastases to the para-aortic lymph nodes, adnexal structures, and upper abdomen are more frequent in stage II than stage I lesions.[99-103] The role of extended para-aortic or whole abdominal irradiation for patients with stage II disease has not yet been defined, however. Because preoperative radiation therapy in endometrial cancer may undertreat occult metastases, a reasonable approach in stage II lesions in premenopausal patients is to do a primary surgical procedure, surgical staging, and then to individualize the extent and fields for postoperative irradiation. The operation should be done only if the parametrial tissues are free of disease. It should include a modified radical hysterectomy, a bilateral salpingo-oophorectomy, pelvic and abdominal peritoneal washings, resection of grossly enlarged pelvic or para-aortic nodes, resection of high common iliac and lower para-aortic lymph nodes, and an omental biopsy. The results of the surgical staging can be used to apply selectively external postoperative irradiation, with or without intracavitary irradiation.

Stage III. Patients were formerly classified as having a clinical stage III endometrial carcinoma if the results of an examination suggested parametrial, pelvic side-wall, or adnexal involvement.[104] Although preoperative adnexal masses may suggest extension of the cancer to these structures, the actual surgical stage may in fact be lower if a benign adnexal pathologic condition is documented. On the other hand, microscopic adnexal metastasis is found at laparotomy in 5% to 10% of patients who have disease confined to the uterus and cervix. A five-year survival of 40% has been reported for patients with surgical stage II disease, compared with only 16% for patients with the former clinical stage III.[105] Another study documented a five-year survival of 80% when metastases were found in only the adnexa, compared with only 15% when metastases had extended to other extrauterine pelvic structures.[106] Thus, the use of surgical staging greatly improves the accuracy of documenting the extent of disease in these patients.

Whenever feasible, the treatment of stage III endometrial carcinoma should include a total abdominal hysterectomy and bilateral salpingo-oophorectomy. An exploratory laparotomy should be done initially to determine the stage of the disease and to resect metastatic disease. In patients with parametrial extension, external irradiation or intracavitary irradiation, or both, can be done preoperatively.

Surgical removal of all visible tumor is important for all patients with stage III disease. The operation should include the removal of enlarged lymph nodes and of all macroscopic disease from the pelvis. In patients without visible evidence of upper abdominal disease, a thorough surgical staging is indicated.

Whole abdominal irradiation has been suggested to treat patients with stage III endometrial cancer, particularly those with positive peritoneal washings or microscopic metastases to the upper abdomen.[107] Because whole abdominal irradiation leads to substantially more morbidity than pelvic irradiation, its use is limited.

Cytotoxic chemotherapeutic agents have not been documented to be of value as adjuvant treatment of stage III endometrial cancer. Furthermore, most patients with advanced stage disease have poorly differentiated tumors, and the response to progestins is also infrequent.

Stage IV. Stage IV endometrial carcinoma is uncommon. In one series, pulmonary metastases were the most frequent

site of metastasis beyond the pelvis, with 40% of patients having lung metastases.[108] Overall, the frequency of pulmonary metastases among patients with endometrial cancer is only 2% to 3%.[109]

The treatment of metastatic disease should be individualized; a combination of surgical excision, radiation therapy, chemotherapy, and progestins is used. Surgical therapy is used to remove the pelvic tumor and to palliate bleeding, discharge, and bowel and bladder problems. Control of the pelvic malignancy can be accomplished in about 30% of patients with either pelvic irradiation or surgical intervention plus pelvic irradiation.[108] Pelvic exenteration is of limited value because most patients with disease spread to the bladder, rectum, or both, will also have distant metastases.

Recurrent disease. The five-year survival of patients with all stages of endometrial cancer is 68%.[110] Risk factors for disease recurrence and death include higher stage and grade of disease, myometrial and adnexal extension, and lymph node metastases.

The treatment of recurrent endometrial cancer should be recommended based on the patient's general medical status and the extent of metastases. Patients with evidence of extrapelvic disease can be treated with progestin. If the metastatic disease is progressive, cytotoxic chemotherapy may be used, although this should be selective because the results of treatment with cytotoxic agents are poor.

The treatment of isolated vaginal metastases is most effective with irradiation. In one series of ten patients with a vaginal recurrence, seven had an isolated vaginal recurrence, whereas only one had vaginal and extrapelvic recurrences.[111] Most of the vaginal recurrences are in the proximal half of the vagina. Patients with a vaginal recurrence should be thoroughly investigated to exclude any metastatic disease. If no metastases are detected, external pelvic irradiation plus some type of brachytherapy may be used in previously untreated patients.

Progestational agents are frequently used to treat recurrent endometrial carcinoma; overall response rates of 30% to 37% have been reported.[112] Parenteral progestin therapy has been shown to result in prolonged survival; the median survival of responding patients is about two years compared with six months for patients who fail to respond.[112] Patients whose lesions are well differentiated tend to respond more frequently than those whose lesions are poorly differentiated. Patients with metastases in the lung, vagina, lymph nodes, or soft tissues are more likely to respond, whereas those with extensive pelvic recurrences rarely do. There is a correlation between the progesterone receptor content of endometrial tumors and the response to progesterone therapy[113,114]—that is, the higher the content of progesterone receptor, the more likely a response will be observed.

Although progestins have been used widely, there is no evidence that any specific type is best. Those most commonly used include hydroxyprogesterone caproate (Delatutin) or medroxyprogesterone acetate (Depo-Provera). Oral megasterol acetate (Megace) is more convenient and produces similar results. Patients are given a daily oral dose of 80 to 320 mg until recurrence or metastases develop.

Another endocrine therapy is tamoxifen,[115,116] which has some activity. Response rates of 30% to 39% have been reported for tamoxifen; most responding tumors have been well differentiated. Tamoxifen has been used to induce progesterone receptors before administering progestins in an attempt to increase the response to hormone therapy. The results of using the combination of tamoxifen and progestin, however, were not significantly different from using progesterone alone.[116]

Cytotoxic chemotherapy using single agents for endometrial carcinoma has been studied; agents that have some activity are listed in Table 7.[53] Only doxorubicin hydrochloride, altretamine (hexamethylmelamine), and cisplatin seem to have clearly established activity,[117,118] with overall response rates in 30% to 40% of patients. Doxorubicin (Adriamycin) has been the drug most extensively studied and seems to be active.[119] Cisplatin when used at full doses (100 mg per m^2) produced responses in 46% of patients not previously treated[120] but only a 4% response rate when used as second-line treatment.[121] Combination chemotherapy for advanced endometrial carcinoma using the two most active single agents, doxorubicin and cisplatin, produced higher response rates (30% to 90%).[122,123] One randomized comparison of this two-drug regimen with doxorubicin alone[124] resulted in a 45% response rate for the two-drug combination versus a 20% response rate for the single agent, doxorubicin. A three-drug combination, cisplatin,

TABLE 7.—*Chemotherapy in Endometrial Carcinoma**

Drugs	No. of Patients Responding/ Total Treated	Response Rate, %
Alkylating agents		
Cyclophosphamide	7/33	21
Mechlorethamine HCl (nitrogen mustard)	3/11	27
Antimetabolites		
Fluorouracil	10/43	23
Antitumor antibiotics		
Doxorubicin (Adriamycin) HCl	33/92	36
Bleomycin sulfate	3/8	37
Miscellaneous		
Altretamine (hexamethylmelamine)	6/20	30
Cisplatin	11/26	42
Cisplatin	4/13	31

HCl=hydrochloride

*From Berek et al.[53]

TABLE 8.—*Survival by Stage in Carcinoma of the Endometrium**

Stage	Total Patients	5-Year Survival No.	5-Year Survival %
I	10,285	7,729	75.1
II	1,885	1,089	57.8
III	844	253	30.0
IV	852	48	10.6
No stage	115	73	63.5
Total	13,981	9,192	65.7

*From the International Federation of Gynaecology and Obstetrics.[68]

TABLE 9.—*Survival by Histologic Grade and Stage in Stage I and II Carcinoma of the Endometrium**

Histologic Grade	Stage I Patients, No.	Stage I 5-Year Survival No.	Stage I 5-Year Survival %	Stage II Patients, No.	Stage II 5-Year Survival No.	Stage II 5-Year Survival %
1	3,665	2,918	79.6	464	298	64.2
2	2,287	1,678	73.4	412	249	60.4
3	866	508	58.7	278	121	43.5
Not graded	1,017	738	72.6	198	106	53.5
Adenosquamous or clear cell	282	199	70.6	95	52	54.7

*From the International Federation of Gynaecology and Obstetrics.[68]

adriamycin, and cyclophosphamide, resulted in a 45% response rate in 209 patients.[125] Another study with the same three drugs produced a 58% overall response rate with a 28% complete response rate.

Survival

The most extensive survival data are recorded in the Annual Report on the Results of Treatment in Gynecological Cancer[68] and are shown in Tables 8 and 9. The data presented in Table 9 reflect the significance of the tumor grade; for example, patients with stage II grade 1 tumors having a better prognosis than patients with stage I grade 3 lesions. Survival relative to the histologic grade and depth of myometrial invasion for stage I disease is shown in Table 8. The five-year survival of deeply invasive, poorly differentiated lesions is only 26%. Survival for stage I endometrial cancer in relation to the various histologic types is shown in Table 9. Adenosquamous, papillary serous, and clear cell carcinomas have a poor prognosis compared with adenocarcinomas.

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YOU ARE NEVER MENTIONED IN MY POEMS:

It is as if when I go back to them
I leave you outside, parked in a car
With the engine idling or else turned off,
Saving fuel.

Wait here, Grandfather always said,
I don't know what I'll find inside.
Grandmother and I sat there
In a green Hudson, weighed down
By Arkansas heat. We didn't get out,
Not even to pick berries:
There were snakes in the ditches,
And chiggers in the tall dry weeds.

Inside, black satchel unfolding,
Grandfather drained wounds or
Delivered babies. Sometimes
The patient was dead before he got there.
He never knew what he'd find,
Brought 'round by a tapping at his door,
The only doc who'd go,
And even he didn't know why
He kept going out into the country
When they didn't call him till too late
Most of the time anyway—

Any more than I know why
I keep going into the poems,
Not knowing what I'll find,
But just enough sense to say
That you have to stay outside
In case it's catching or
Too terrible for your eyes.

MARGARET KAUFMAN
Kentfield, California

Clozapine—A New and Different Neuroleptic

Discussants
ELLEN HALLER, MD, *and* RENÉE L. BINDER, MD

These discussions ore selected from the weekly stoff conferences in the Department of Medicine, University of Californio, Son Froncisco. Token from o tronscription, it has been edited by Homer A. Boushey, MD, Professor of Medicine, ond Nathon M. Boss, MD, PhD, Associote Professor of Medicine, under the direction of Lloyd H. Smith, Jr, MD, Professor of Medicine ond Associote Deon in the School of Medicine.

EDITOR'S NOTE: *Discussions for this section of the journal ore usually selected from presentotions mode ot the weekly staff conference in the Department of Medicine at the University of California, San Francisco (UCSF). Occasionally, however, a presentation made in another department's staff conference oppears sufficiently important to the general medicol community to warrant wide disseminotion. This stoff conference is an example. The UCSF Deportment of Psychiatry recently devoted o conference to the discussion of clozapine, a new neuroleptic agent whose remarkable effectiveness in schizophrenia resistant to other treatments guarontees thot it will be widely given, but whose potential side effects are so grave that they should be known by oll physicions providing primary or consultative care for medicol disorders in patients with psychiatric illness.*

RENÉE L. BINDER, MD*: *Many patients with schizophrenia remoin symptomatic despite treatment, and many others ore intoleront of currently available neuroleptic drugs. Ellen Haller, MD, will discuss the clinical and psychopharmacologic properties of clozapine, o new neuroleptic ogent released by the Food ond Drug Administration in February 1990. Extensive clinical trials have shown that clozopine has clinical superiority over other neuroleptics. Dr Haller will review practical guidelines for initiating treatment with clozapine and will present coses that illustrate its clinical profile. In addition, I will discuss clozapine's adverse effects and their management.*

ELLEN HALLER, MD†: Despite treatment with available neuroleptic agents, it is estimated that 10% to 20% of schizophrenic patients remain symptomatic.[1] In addition to those patients who are refractory to treatment, many others cannot tolerate currently available neuroleptics because of their adverse effects, particularly the induction of neurologic symptoms.[2] Clozapine, a dibenzodiazepine, is a new drug for schizophrenia that appears to have some advantages over other neuroleptics. It is currently marketed in more than 20 countries worldwide. Until recently, clozapine was available only for investigational and compassionate use in the United States. The purpose of this report is to alert physicians to this new drug that has just been released by the Food and Drug Administration.

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Clinical and Psychopharmacologic Properties

Several studies have shown clozapine's efficacy in treatment-resistant schizophrenia.[3-6] A recently published study reported a statistically significant difference in the efficacy of clozapine and chlorpromazine when these drugs were compared in a multicenter, double-blind trial.[3] Of the treatment-refractory schizophrenic patients treated with clozapine, 30% were categorized as responders as opposed to only 4% of those treated with chlorpromazine.[3]

In addition to its superior clinical efficacy, clozapine appears to suppress abnormal involuntary movements[7-9] and has been shown to have a lower propensity to cause extrapyramidal symptoms, possibly including tardive dyskinesia.[10]

Clozapine seems to have a mechanism of action different from that of standard antipsychotics. In animals, it fails to induce the typical effects of dopamine-receptor blockage. Unlike traditional neuroleptic agents, clozapine does not induce catalepsy, antagonize amphetamine-induced stereotypes, or increase D_2-receptor hypersensitivity.[4,11] It acts at mesolimbic dopamine receptors but appears to have lower affinity for nigrostriatal dopamine receptors.[12] In addition, rates of dopamine turnover when measured by the concentration of its metabolite, homovanillic acid, differ when haloperidol and clozapine are compared.[13] Clozapine has been found to increase only weakly the conversion of dopamine to homovanillic acid, suggesting weaker dopamine-receptor blockage.[13] Finally, unlike other antipsychotic drugs that typically induce a sustained elevation of serum prolactin levels, clozapine provokes only minimal and transient increases, further supporting the hypothesis that clozapine exerts a different action at dopamine receptors than do standard neuroleptics.[14,15]

In addition to its effects on the dopamine system, clozapine has serotonergic (S_2), adrenergic (α_1), histaminergic (H_1), and muscarinic cholinergic receptor antagonism.[16-18]

Practical Guidelines for Initiating Treatment

Clozapine is about twice as potent as chlorpromazine. The average therapeutic dosage is 300 to 450 mg per day, although it can be titrated to as much as 600 mg per day or even 900 mg per day in certain cases.[3] Clozapine therapy is typically started by giving a test dose of 25 mg followed in an hour by measuring the patient's orthostatic changes in blood pressure and heart rate. If there is no significant orthostasis, a regimen of 25 mg three times a day orally is

(Haller E, Binder RL: Clozapine—A new and different neuroleptic. West J Med 1990 Jul; 153:62-64)

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begun. The dosage is then increased by 25 mg per day as tolerated until a therapeutic response is seen or until it reaches 600 mg per day. As we describe later, increases above 600 mg must be made even more cautiously because of an increased risk of seizures. If the patient is orthostatic, however, the medication dosage is titrated upward at a slower rate of 25 mg every two or three days, as tolerated.

Clinical Examples

At our center at the University of California, San Francisco, we have treated a total of 19 patients with clozapine in an open trial. All patients enrolled met the criteria of the *Diagnostic and Statistical Manual of Mental Disorders,* third edition, revised, for schizophrenia and were either refractory to or intolerant of treatment. Patients were defined as refractory if they had continued substantial psychotic symptoms despite trials of at least two marketed neuroleptic drugs at dosages equivalent to 1,000 mg per day of chlorpromazine for at least six weeks. Patients were defined as intolerant if they had severe tardive dyskinesia or severe extrapyramidal symptoms—acute dystonias, parkinsonism, or akathisia—unresponsive to standard interventions. The following cases were selected for presentation because they illustrate clozapine's clinical profile and are representative of the overall patient sample.

Case 1

The symptoms of schizophrenia have been classified as either positive or negative. Positive symptoms include loose associations, hallucinations, delusions, bizarre behavior, and pressured speech.[19(p261)] This case shows clozapine's ability to treat the positive symptoms of schizophrenia in a treatment-resistant patient.

The patient, a 19-year-old man, had had psychosis for three years, manifested by poor personal hygiene, intermittent pressured speech, agitated behavior, depressive periods, looseness of associations, flight of ideas, ideas of reference, auditory hallucinations, religious and grandiose delusions, suicidality with bizarre suicide attempts (such as inserting a paper clip into a wall socket), somatic preoccupations, and impaired insight. Because of these symptoms, the patient had been treated with various psychotropic drugs in different combinations including thioridazine hydrochloride, trifluoperazine hydrochloride, thiothixene, haloperidol, perphenazine, loxapine, imipramine hydrochloride, nortriptyline hydrochloride, desipramine hydrochloride, diazepam, lorazepam, alprazolam, lithium carbonate, carbamazepine, and valproic acid. Despite adequate trials of these medications, he remained symptomatic and in need of acute or subacute hospital care. When admitted for the initiation of clozapine therapy, he was taking loxapine, 350 mg per day; desipramine hydrochloride, 100 mg per day; and lorazepam, as much as 10 mg per day, and was floridly psychotic. These drugs were tapered, clozapine therapy was begun, and the dosage was titrated upward as tolerated. The patient's symptoms began to abate within a week at a total daily dose of 175 mg, and his psychosis continued to clear as the dosage was increased. On a total daily dose of 450 mg three weeks into the trial, he was in excellent behavioral control, engaged appropriately with staff and peers, showed improved grooming and hygiene, manifested a euthymic mood, and was much better organized in his thinking, although he displayed mild tangentiality when discussing affect-laden material. He was no longer delusional but reported brief, intermittent auditory hallucinations. His insight was also improved, and, for the first time since his illness began, he was discharged to a halfway house rather than to a subacute treatment facility.

Case 2

The second case illustrates clozapine's effectiveness on the negative symptoms of treatment-resistant schizophrenia. Negative symptoms include blunted affect, poverty of speech, poor grooming, impaired motivation, social withdrawal, and attentional deficits.[19(p261)]

The patient, a 34-year-old woman, had had chronic undifferentiated schizophrenia for 19 years, with ten previous psychiatric admissions. Over the years, she had been treated with various combinations of psychotropic drugs including thioridazine, haloperidol, loxapine, fluphenazine, chlorpromazine, trifluoperazine hydrochloride, perphenazine, trazodone hydrochloride, doxepin hydrochloride, maprotiline, lithium carbonate, carbamazepine, and alprazolam. Despite adequate trials of these medications, she continued to experience symptoms of psychosis, including bizarre grooming and dress, avoidance of eye contact, pronounced social withdrawal, blunted affect, looseness of associations, constant auditory hallucinations to which she would respond, suspiciousness, and bizarre mannerisms. After a two-month stay in hospital with withdrawal of other medications and a gradual upward titration of the dose of clozapine to 750 mg per day, many of these symptoms abated. The patient behaved more appropriately in groups, was much more engageable, reported fewer hallucinations, and showed a broader range of affect. Of note, she continued to improve at a slow but steady rate over time as an outpatient.

Case 3

This case is of a patient with severe tardive dyskinesia whose neurologic symptoms reversed dramatically with clozapine treatment.

The patient, a 37-year-old man, had had chronic paranoid-type schizophrenia for 21 years, with 19 acute psychiatric hospital admissions. He had been treated in the past with various combinations of trifluoperazine hydrochloride, haloperidol, chlorpromazine, thiothixene, perphenazine, pimozide, lithium carbonate, carbamazepine, and lorazepam. For approximately eight years, he manifested symptoms of an involuntary movement disorder that affected primarily both upper extremities. The coarse, rhythmic, low-frequency tremor was so severe that it impeded his ability to feed himself and exacerbated his social isolation. Additional ongoing psychotic symptoms included chronic auditory hallucinations, blunted affect, and paranoid ideation. On hospital admission, his medication doses of lithium carbonate, 900 mg per day; pimozide, 38 mg per day; perphenazine, 36 mg per day; and lorazepam, 9 mg per day, were tapered with a resultant worsening of both his psychosis and movement disorder. Within three weeks of initiating treatment, the patient was taking 450 mg per day of clozapine, and both the psychosis and the movement disorder diminished dramatically. At the time of discharge, he had minimal symptoms of tardive dyskinesia, denied auditory hallucinations, was engageable in group situations, and appropriately initiated conversations with staff.

Adverse Effects

Dr Binder: Despite its clinical effectiveness, clozapine's side effects delayed its release in the United States for many years. In a large multicenter study in which 126 patients received clozapine, the most commonly reported side effects were drowsiness in 21%, tachycardia in 17%, consti-

pation in 14%, hypotension in 13%, benign fever in 13%, and hypersalivation in 13%.[3] Of the 19 patients treated so far at our center, 15 have had intermittent resting tachycardia, and 12 have had intermittent orthostatic hypotension. In addition, 15 have complained of sedation. These side effects have limited the rapidity with which the dose of clozapine can be increased into the therapeutic range. Nevertheless, all of our patients tolerated the use of clozapine with gradual normalization of their vital signs.

Most worrisome are the serious adverse effects of agranulocytosis and the increased incidence of seizures. Until now, the experience in this country has been of a 2% cumulative incidence of agranulocytosis after 52 weeks of treatment.[3,20] The risk is not related to age, sex, or dose, and the majority of cases have occurred between the 6th and 18th weeks of clozapine treatment.[3,21] The clinical pattern of cases and bone marrow findings suggest that an immune mechanism may underlie the agranulocytosis.[21] So far there have been no reported deaths from clozapine-induced agranulocytosis in the United States, and all cases have resolved after the drug was discontinued (data on file, Sandoz Pharmaceuticals). Given the high incidence of agranulocytosis associated with clozapine use, however, weekly monitoring of each patient's complete blood count is essential. Of the 19 patients treated with clozapine at our center, granulocytopenia developed in 1. Complete blood counts done weekly showed a gradual decline in this patient's leukocyte count, and when it fell to 2×10^9 per liter with 0.40 granulocytes, we discontinued clozapine. We then checked his complete blood count daily, and within six days, it had returned to normal with a leukocyte count of 8.1×10^9 per liter with 0.66 granulocytes. At no time was the patient physically ill during this period, his vital signs remained within normal limits, and he did not require admission to hospital. He had taken clozapine for a total of six months before manifesting granulocytopenia.

Sandoz Pharmaceuticals has reported an increased risk of grand mal seizures in patients without seizure histories receiving more than 600 mg per day of clozapine (data on file, Sandoz Pharmaceuticals). A definite dose-related pattern is described with a comparative risk rate of 5% for high dosage (600 mg per day and higher), 3% to 4% for medium dosage (300 to 599 mg per day), and 1% to 2% for low dosage (up to 300 mg per day). At our institution, one patient (with no history of a seizure disorder) had a grand mal seizure three days after his clozapine dosage was increased from 575 to 600 mg per day to control continued psychotic symptoms. His baseline electroencephalogram taken before the increase had been normal, as was a repeat electroencephalogram. Because he had improved clinically on clozapine, he asked that the treatment be continued. We therefore decreased his clozapine dosage and began maintenance treatment with phenytoin after an initial loading dose. To date, the patient remains in treatment and is stable on this combination regimen of clozapine and phenytoin. The management of patients taking clozapine in whom seizures develop is complicated, but this adverse effect does not contradict further use of the drug if indicated.[22]

Conclusion

Clozapine is an exciting new drug for the treatment of schizophrenia. The major differences between it and standard neuroleptic agents include its apparent superior clinical efficacy and its low propensity to induce extrapyramidal symptoms or tardive dyskinesia. In addition, it appears to have a different mechanism of action, and further study of its neurochemical effects may help elucidate the mechanisms of schizophrenia. A substantial risk of agranulocytosis and seizures is associated with clozapine use, so it has been approved only for use in patients with severe schizophrenia in whom trials of standard neuroleptics have failed because of inadequate clinical response or dose-limiting adverse effects. Although physicians may want to prescribe it for newly diagnosed schizophrenia or even in patients with other psychoses, clozapine's toxicity precludes its use for all but the most severely impaired schizophrenics.

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Extracorporeal Shock Wave Lithotripsy of Urinary Calculi

Theory, Efficacy, and Adverse Effects

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This paper was chosen as the winner of THE WESTERN JOURNAL OF MEDICINE's 1990 Medical Student Writing Competition. The contest was open to all students attending medical schools in the West and will be repeated annually.

LINDA HAWES CLEVER, MD
Editor

Extracorporeal shock wave lithotripsy (ESWL) for the treatment of upper urinary tract stone disease is held in high regard by the public and the profession. Although the efficacy is good (77.4% to 100%) for the treatment of 1- to 2-cm stones in select patients, ESWL may require the assistance of adjuvant procedures in as many as 26% of patients and may need repeating in as many as 32% of patients. These represent more difficult situations in which larger, more numerous, or harder stones may be present and in which ureteral stones are manipulated before treatment. The predominant adverse effect of ESWL treatment is the microvascular disruption of the tissues through which the shock waves pass. In addition, the procedure is painful, with many patients requiring narcotic analgesia. Long-term complications such as the new onset of hypertension have occurred in as many as 8% of treated patients, but much speculation about the long-term effects remains.

(Kelley JM: Extracorporeal shock wave lithotripsy of urinary calculi—Theory, efficacy, and adverse effects. West J Med 1990 Jul; 153:65-69)

Often in medicine, the benefits gained from a therapeutic intervention are weighed against the risks of carrying out that intervention. A simple balance between gains and losses, or present effects and future results, exists that teeters between both outcomes. Such may be the case with extracorporeal shock wave lithotripsy (ESWL).

Since its first clinical application in 1980, ESWL's technologic progress has advanced at a sprinter's pace. Currently more than 300 extracorporeal lithotripters are used in 32 countries worldwide and more than 500,000 people have received shock wave treatment of renal or ureteral stones.[1,2] Despite this clinical experience, fundamental questions still remain about the nature of shock wave energy, its effects on the tissues through which it passes, the proper dosage, and the absolute role of ESWL in the treatment of stone disease.

With the procedure embraced by both the public and the profession, the fervor to develop new, less costly, and safer devices for delivering shock waves has made keeping track of the players and the styles of play difficult. The Dornier company, from which pioneering lithotripsy studies were generated and the producer of the first clinically available extracorporeal shock wave lithotripter, the HM-1, has found itself among an ever-increasing pack of rookie companies trying to capture a portion of the growing market. With the increased competition and the rapidly expanding body of knowledge, new variants of extracorporeal shock wave-generating devices have been emerging almost yearly. As an example of just how quickly things are progressing, since its development of the HM-1 nearly a decade ago, the Dornier company has produced the HM-2, HM-3, HM-4, MPL 9000, and MFL 5000 models.[2]

With the newer, second-generation lithotripters, attempts have been made either to improve on the original design or to develop novel approaches to the task of stone fragmentation. The changes made in various lithotripter components include variations in the energy source, focusing devices, coupling medium, and stone localization systems.[2]

Shock Wave Principles

Although highly theoretical, current thinking regarding shock wave behavior holds that, in the spark-gap type of shock wave generator, the sudden jump of charge between two electrodes immersed in deionized water results in the instantaneous evaporation of water around the electrodes. This sudden evaporation creates an expanding gas bubble that compresses the surrounding water medium and produces an increase in the adjacent water density.[3] Resisting further compression, the water medium allows transmission of the propagated pressure wave at an increased velocity. This change in velocity results in the characteristic shock wave appearance of a sharp pressure rise followed by a gradual decay.[4]

Because of a stone's ability to effectively resist compression, it is thought that tensile forces cause the characteristic peeling off of outer layers that has been observed to occur with fragmentation. The tensile forces are essentially the result of reflected and refracted shock waves, which develop an area of low pressure behind them as they journey away from the area of contact. These tensile forces are thought to stress the stone's intrinsic ability to resist longitudinal stretching, resulting in the formation of fractures from the outermost surface inward.[4] In the spark-gap type of lithotripter machines, the strength of the administered shock waves can generally be varied by changing the voltage (about 18 to 24 kV) across the spark-generating electrode.[4]

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ABBREVIATIONS USED IN TEXT

ESWL = extracorporeal shock wave lithotripsy
NAG = β-*N*-acetyl-D-glucosaminase

Cellular Effects of Shock Waves

At the cellular level, investigation with high-energy shock waves has been mainly in the study of their potential for use against neoplastic cell lines. These studies, however, could serve partly as an analysis of their effects at the cellular level.

In a study using rat prostate carcinoma cells and human melanoma cell lines in vitro, Russo and co-workers observed a selective diminution of cells in the G2 and M phases of the cell cycle following exposure to 800 to 1,500 shock waves. The complementing in vivo study showed a delay in tumor growth among cells treated directly in an animal host or treated before injection into an animal host.[5] The finding of a shock wave-induced antiproliferative effect has been supported by the work of others, but the selective cell phase diminution was not observed.[6]

Similarly, Randazzo and associates examined indices of cell viability, growth, cell attachment, and electron-microscopic appearance in renal carcinoma cells versus normal human embryonic kidney cells[7] in vitro. The renal carcinoma cells were treated with 1,400 or 2,000 shock waves at 18 kV, causing a notable decrease in viability, growth, and attachment over what was observed in the normal human embryonic kidney cells. Electron microscopy showed substantial damage to both cell types with improvement seen in both at 120 hours when given the lower shock wave dose, but favoring the embryonic kidney cells morphologically.[7] In vivo experimentation using FANFT, a carcinogen-induced mouse bladder tumor transplanted into the hind legs of C3H/He mice and exposed to 1,400 shock waves, showed an inhibitory effect on tumor growth at this dose.[7]

Showing obvious cellular effects, these study results also raise the question of cell vulnerability at particular cell cycle phases. They suggest also that some cells, when damaged, may have the capability to undergo repair after exposure to shock waves.

Concerning normal cell lines, pioneering work by Chaussy demonstrated no in vitro change in leukocyte number or function following shock wave exposure.[8] In a study by Yang and associates, however, a significant cytotoxic effect was observed in bone marrow cells exposed in vitro. This effect was observed to be dose dependent with increasing shock wave exposure: As few as 500 shock waves at 18 kV decreased cell viability by 50%. In addition, colony-forming ability was reduced following exposure to shock waves.[9]

Admonishing the cautious interpretation of tumor cell studies, Laudone and colleagues showed that the air-fluid interface present in containment vessels used for in vitro studies significantly enhanced the cytotoxic effects of administered shock waves. They noted, too, that shock wave effects differ substantially for cells in suspension versus cells in tissue, making comparisons difficult. Furthermore, in trying to reproduce the antiproliferative effects observed by other investigators, using the implantation of AT3 tumor cells, they witnessed no significant change in tumor doubling times versus controls after treatment of the tumors with 1,000 shock waves at 24 kV. They concluded from the latter study, however, that the choice of tumor type may have been inappropriate. The AT3 type is homogenous, lacking the surface areas of a more variegated tumor.[10]

Tissue Effects: Animal Studies

Preliminary studies showed that shock waves pass through living tissue with little attenuation in wave energy.[8] Work with animal models and in vitro systems suggested that shock waves produce only minimal degrees of tissue injury that resolves quickly. An early study by Chaussy involving the surgical deposition of a calculus into the renal pelvis of 17 dogs with subsequent fragmentation showed successful fragmentation and fragment clearance in 13 of the animals, each given 500 shock waves, without evidence of tissue injury or loss of renal function.[8] Notable exceptions, however, were the massive alveolar and vascular rupture produced in directly exposed rat lung and, separately, hemolysis of erythrocytes exposed in vitro to shock waves.[8] The former led to the practice of shielding the lung during treatment, and the latter was attributed to the presence of aged erythrocytes in the test blood specimen.

Allowing gross and histologic examination within and adjacent to the focus of maximum shock wave energy, continued studies in animals have played a necessary part in assessing the effects of high-energy shock waves on living tissues. Animal subjects used to date include rats, rabbits, dogs, and pigs.

In studies of rats, Recker and co-workers showed by scanning electron microscopy of treated kidneys the diffuse loss of microvilli and ciliae on the cell surface of tubules, cell vacuolization, desquamation, and sporadic glomerular rupture.[11] In studies of the ovary, an organ likely to receive shock waves during the treatment of distal ureteral calculi, no important effects on follicle number or fertility were noted in female rats with exposure to 1,500 focused shock waves at 15 kV.[12] Given the possibility of unintentional vertebral shock wave exposure in children undergoing ESWL, the proximal tibia of 5-week-old rats was submitted to 1,500 shock waves at 20 kV, and the animals were killed two, four, and ten weeks after treatment. Focal growth plate dysplasia was found in 8 (44%) of the 18 rats when compared with age-matched controls, with 2 (33%) of the 6 ten-week animals showing extensive, rather than focal, dysplasia.[13]

For a general assessment of acute and chronic effects of ESWL on various tissues, Graff and associates, using the rabbit model, observed posttreatment bleeding and ulceration of the exposed rectum, intermuscular and intramuscular hematomas, and subperiosteal bleeding at 48 hours. Chronic effects, apparent at one to two months, included aseptic marrow necrosis, damage to osteocytes, and evidence of bone remodeling.[14] Study of the morphologic and functional effects of 3,000 shock waves (at 20 kV) on the rabbit kidney showed the acute (seven days) changes of focal subcapsular hemorrhage, tubular dilatation, and interstitial hemorrhage; chronically (two months), only focal interstitial fibrosis was seen. When both kidneys were assessed for kidney functional losses, the only significant findings were a transient four-day decrease in creatinine clearance and a transient three-day increased concentration of urinary free hemoglobin, both of which returned to baseline.[15]

Several studies have examined the direct effects of shock waves on the kidney, using the canine model. In contradistinction to the early findings of Chaussy, Brendel showed renal hemorrhages (as much as 0.5 cm in size), interstitial edema with interstitial widening, and renal capsule petechiae following shock wave exposure to the canine kidney.[16(p141)] To study the acute and chronic effects on the kidney and try to correlate shock wave dose with degree of

injury, Newman and colleagues studied six kidneys of mongrel dogs. The acute-effects group comprised four kidneys, each having exposure to a different shock wave dosage (1,776, 4,500, 6,000, and 8,000 shocks), and the animals were killed at 48 to 72 hours. Corticomedullary hemorrhages were found universally in the kidneys of this group, especially involving thin-walled vessels. Three of four kidneys (75%) also showed perirenal hemorrhage or hematoma. The chronic-effects group—two kidneys exposed to 1,600 or 8,000 shock waves and the animals killed 30 days after treatment—showed evidence of fibrosis, which was smaller in the less heavily treated kidney. Surprisingly, neither kidney in the acute or chronic group exposed to 8,000 shock waves showed complete necrosis. All kidneys, whatever dose given, sustained modest injury.[17] The unusually high shock wave dosages given in this experiment were for assessing extremes in dosage and effects.

Using more conventional shock wave dosages, other studies have examined shock wave exposure to kidneys for acute and chronic changes.[18-20] After 1 to 24 hours, macroscopic changes include perirenal fat hemorrhages, a relative increase in treated kidney size, subcapsular hematomas, overlying muscle hemorrhages, and hemorrhages of the renal parenchyma, capsule, or hilum.[18-20] On histologic examination there were focal and diffuse interstitial hemorrhage, venous thrombosis involving arcuate and interlobular veins, and tubular dilatation.[18-20] Chronic changes (seven days to three months) were not observed macroscopically.[19,20] On histologic examination, chronic renal changes included only focal areas of streaky fibrosis and calcium deposition.[19,20] By electron microscopy, the microvascular wall was the site of the greatest injury.[18] When assessing shock wave dose effects, injuries were more serious above 500 shocks, but no difference was appreciable when comparing the effects of 1,500 with 3,000 shock waves.[18]

Pig model studies, too, have shown renal structural disruption with exposure to high-energy shock waves. Thinking pigs to be a better model for human kidney than other model kidneys, Muschter and co-workers showed acute renal injury consisting of perirenal and intrarenal hematomas, renal parenchymal damage, and parenchymal necrosis following renal parenchymal ESWL treatment.[21] Chronic changes were demonstrated by Begun and Laswon, who examined pig kidneys four weeks after treatment.[22] They found focal scarring in the treated kidney circumscribed by marginally vascularized areas of injury in which interstitial and perivascular fibrosis, partial glomerular hyalinization, and tubular injury were present, resembling end-stage renal disease.[22] The mechanism(s) of shock wave-induced tissue injury has not yet been elucidated. Under consideration have been the compressive and tensile forces of the wave, thermal events, free radical effects, or a cavitation phenomenon.

Direct forces are a plausible explanation for such injury in biologic structures having different impedances, but thermal injury is unlikely.[23] Free radicals produced by high-energy shock waves may play a role in cytotoxicity. They have, however, shown little effect on a target cell assay when compared with those of cobalt 60 origin.[24] A cavitation phenomenon seems the most widely accepted explanation for observed tissue effects.[3,5,23] Sometimes called pseudocavitation, it is the product of small gas or vapor bubbles by rapid pressure changes in a liquid.[25] A momentary decrease in pressure behind an advancing shock wave is thought to cause local vaporization within a liquid, or undissolution of a dissolved gas, producing tiny bubbles. Such bubbles have been observed in in vitro experiments. It is the motion of these bubbles that could cause tissue injury.[23,25]

Clinical Experience

Reports of clinical success with ESWL abound in the literature. Since its first clinical application nearly a decade ago, widespread acceptance has provided the opportunity to review the experience in a sizable population of treated patients.

Regarding efficacy, early studies by Chaussy and associates, in which 945 patients were treated over a three-year period, showed that 89.5% of treated patients were stone free at three months' follow-up.[26] In the United States Cooperative Study of Extracorporeal Shock Wave Lithotripsy, follow-up of 739 treated cases at three months showed freedom from stones and all detectable residual fragments in 77.4% of cases.[27] Overall, the estimated efficacy of ESWL ranges from 38% to 100%. Some of this variation is attributable to the treatment of difficult and large stones, a significant number of patient retreatments, and the assistance of adjuvant procedures.

It has been suggested that a single kidney stone with a largest diameter of 2.0 cm or as many as three stones of less than or equal to 1.0 cm provide an excellent target for ESWL.[28] Such was supported in the US cooperative study in which the model size of treated stones was 1 to 2 cm.[27] In dealing with large stones, Roth and Beckman found that only 38% of patients with calculi larger than 3.0 cm are treated successfully by ESWL monotherapy.[29] In the US cooperative study, most patients required a single ESWL treatment, but one, two, and more treatments were required in 16%, 14%, and 2% of patients, respectively.[27]

The use of percutaneous or endoscopic procedures as an adjuvant to ESWL therapy is commonplace. In some studies, these procedures have been used routinely in as many as 26% of patients to reposition a stone, remove an excessive fragment burden following treatment, or allow calyceal drainage of urine.[30,31] Overall success rates, too, have improved with adjuvant therapy. In one study, treatment using ESWL alone was 80% successful, climbing to 90% at three months' follow-up with the addition of adjuvant measures.[32] In many cases, the stone burden is the key factor in determining whether assistance is necessary, as the increased number of fragments released from a large (> 3.0 cm) stone or numerous stones raises the risk of urinary tract obstruction.[31] In addition, the variable success of in situ ureteral stone fragmentation has been improved by the pretreatment manipulation of ureteral stones into a more advantageous position in the renal pelvis.[33-35]

Adverse Effects

Complications seen routinely with ESWL treatment of stone disease are cutaneous petechiae or subcutaneous hematomas at the shock wave entry and exit sites (especially in thin patients) and costovertebral angle or lower quadrant pain, with as many as 40% of these patients requiring narcotics for pain relief.[36] Gross hematuria is observed immediately in virtually all patients and typically resolves by 24 to 48 hours after treatment.[3,36,37] Obstruction of urinary flow by fragments also occurs, with a general frequency of between 6% and 25%.[33,38,39] The piling of stone fragments in the ureter, called steinstrasse, has been described throughout the literature and in one study occurred in 5% of 600 patients.[32] After large or infected stones are fragmented, infection can develop in an obstructed calyceal system, resulting in septicemia. Such complications have occurred in less than 5% of the cases examined.[32,38,40]

Other complications include pneumonitis in 1.2% of patients,[27] prolonged ileus in 10%,[32] and transient pyrexia in 30% of patients.[32] Perirenal hematomas, occurring in as many as 2.5% of patients in general following ESWL treatment, have been found with greater frequency (as many as 3.8%) in patients with poorly controlled hypertension at the time of treatment.[41]

Morphologically, computed tomography and magnetic resonance imaging have shown significant changes in the posttreatment kidney. Computed tomographic studies acutely reveal a general relative increase in the size of the treated kidney (9% in one study), subcapsular hematomas, intrarenal hemorrhages, small subcapsular fluid collections of an unknown type, and perirenal fascial thickening.[42] Magnetic resonance imaging findings concur; in the examination of 39 kidneys in one study, 29 (74%) showed one or more morphologic changes.[43] In addition, focal or diffuse loss of the corticomedullary junction occurred in 16 (41%) of those 39 patients.[43] Other investigators have observed similar changes.[3,39]

In the investigation for changes in renal function, various methods have been employed. Enzyme studies by Kishimoto and co-workers and Assimos and colleagues have revealed transient elevations in renal tubular enzymes for as long as seven days after treatment.[44,45] Kishimoto and associates observed shock wave dose-related increases in the levels of cell-escaped lactate dehydrogenase, aspartate aminotransferase, and free hemoglobin lasting as long as four days in serial blood specimens and an increasing β-*N*-acetyl-D-glucosaminase (NAG) and creatinine clearance trend through the completion of the observation period (day 4).[44] Assimos and co-workers noted an increase in the urine concentrations of the proximal tubule and brush border enzymes NAG, γ-glutamyltransferase, and β-galactosidase, with peak values reached at day 3 and returning to baseline beginning at five to seven days.[45] Marcellan and Servio also observed increases in serum lactate dehydrogenase and urine NAG levels, but these levels remained within the upper limits of the normal range.[46] Similarly, Schulze and associates measured a fourfold increase in the level of kidney epithelial antigens, using monoclonal antibodies, by the fourth post-ESWL treatment day.[47] These studies suggest that nephron injury does occur, but whether the decrease in some values indicates repair of this injury or progression to a nonfunctional state, without further leakage, is unclear.

Another study by Gilbert and colleagues assessing post-ESWL renal function more traditionally found nephrotic-range proteinuria for three to six months after treatment, but no significant change in the calculated glomerular filtration rate, fractional sodium excretion, or urine osmolality among treated patients.[48] These findings suggest that altered permeability of the glomerular basement membrane occurs with shock wave exposure.

Flow studies, too, have shown changes in effective renal plasma flow following ESWL treatment. Using quantitative radionucleotide renography scans, Kaude and co-workers found a 5% difference in the effective renal plasma flow before and after treatment in 10 of 33 patients.[39] Thomas and colleagues also found a significant difference in the effective renal plasma flow between treated and untreated sides, when greater than 1,600 shock waves were applied to the treated kidney.[49]

With the exception of the flow studies and the rabbit studies of Gunasekaran and associates,[15] these studies have the inherent limitation of being unable to selectively study just the treated kidney. A study by Kulb and co-workers involving patients with solitary kidneys showed a significant posttreatment rise in serum creatinine levels above 177 μmol per liter (2 mg per dl) in only 3 of 68 patients.[50] Given the vast nephron reserve in the kidney, however, a serious injury might not be appreciable simply by examining serum creatinine levels.

Concern over the long-term complications of ESWL treatment has recently been raised. Newly diagnosed hypertension has been found in treated patients. At 6 to 12 months after treatment, Lingeman and Kulb noted among 95 patients an 8% incidence of new-onset hypertension requiring drug therapy and a 15% incidence of new diastolic pressure elevations not requiring therapy.[51] Similar observations were made in two other studies by Newman and associates and Williams and colleagues, each reporting an increased incidence of new-onset hypertension in 8% of 148 and 91 patients, respectively. In both studies, these newly hypertensive patients required treatment.[52,53] In addition, at 17 to 21 months of follow-up, the Williams study also reported a substantial decrease in the effective renal plasma flow of the treated kidney in 21 of 148 treated patients.[53]

Conclusion

As Lingeman and co-workers put it,

> The rapid acceptance and adoption of ESWL has been facilitated by the false perception that this technology is entirely safe and that shock wave treatment does not induce severe, acute or chronic side effects.[37(p797)]

Although the overall mortality associated with this procedure is low (0.02% in a survey of 62,793 patients),[54] the effects of this energy on living tissue require a need for its judicious use.

Of added concern is the problem of repeat stone formation, with the frequency of stone recurrence found in one study to be 50% to 70% of patients,[55] who may undergo repeated ESWL treatments. Such retreatment would be expected to take its toll on a treated kidney. Will long-term accumulated injuries cause premature aging of treated kidneys, resulting in a decreased parenchymal reserve in later years? Although little long-term evidence exists for permanently altered renal function, the substantial nephron reserve of the kidney could conceivably compensate for sizable parenchymal injuries such that these injuries will not be manifested immediately. Effective at fulfilling its purpose, some ESWL models, however, still produce sufficient discomfort in treated patients to require narcotic analgesia. An added factor is that a substantial number of these patients will require additional procedures, endoscopic or invasive, indicating that ESWL alone is not a cure for all stone problems and requires the optimal selection of patients.

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Epitomes

Important Advances in Clinical Medicine

Chest Diseases

The Scientific Board of the California Medical Association presents the following inventory of items of progress in chest diseases. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers, or scholars to stay abreast of these items of progress in chest diseases that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Chest Diseases of the California Medical Association, and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Inhaled Treatment of Asthma

THE TOPICAL DELIVERY OF METERED-DOSE INHALER (MDI) drugs is currently regarded as optimal for the treatment of asthma. The standard dosages of most agents are two to four puffs from an MDI three or four times a day, whereas inhalant solutions of bronchodilators are usually given in dosages that may be ten times as large. Recently there has been a trend towards using an appropriately increased number of puffs of an MDI (usually with a spacer added) for emergency department and inpatient therapy for acute asthma in place of jet-nebulizer aerosolization.

The increasing death rate of asthmatic patients has led to concerns about the role of sympathomimetic aerosols. In New Zealand, the potent aerosol bronchodilator, fenoterol, has been cited as potentially hazardous, but no other MDI preparation has been implicated. Recently airway reactions to the use of metaproterenol sulfate (Alupent) MDI were found to be the result of a change in the adjuvant, and this problem has been resolved by restoring the original formulation.

Corticosteroids are used by some authorities to provide cornerstone therapy for the inflammatory changes that characterize asthma. The appropriate doses and number of treatments a day for various MDI products are controversial, however. It is probable that increased dosage would be effective in some persons with asthma who respond inadequately to standard dosing with inhaled steroids, although the inconvenience and expense are major obstacles. It is claimed that flunisolide is effective if given twice a day, and it is probable that beclomethasone dipropionate and triamcinolone would be equally effective if given twice rather than three or four times a day.

In the outpatient management of asthma, most experts prescribe MDI delivery of a β_2-selective bronchodilator, using increased doses if necessary. A spacer can be advantageous, but some patients prefer the new inhaled powder form of albuterol. A steroid MDI with a spacer can be added, but considerable individual experimenting may be needed to establish the optimal dosing for each patient. Younger patients may benefit from using cromolyn sodium and older ones with a component of chronic obstructive pulmonary disease should try ipratropium bromide. Oral therapy in patients with chronic asthma has a secondary role, but an oral agent should be introduced—choosing from slow-release theophylline or albuterol, or prednisone—if the aerosol regimen becomes too complex or demanding. For a competent adult patient, there is no justification for prescribing a powered nebulizer or an exotic aerosol drug delivery system to be used at home.

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Lasers in Pulmonary Treatment

IN THE PAST DECADE lasers have been developed for the treatment of tracheobronchial obstruction. Evidence gathered by many investigators indicates that the neodymium-YAG [yttrium-aluminum-garnet] laser is most helpful in providing rapid and safe palliative relief of obstructed large airways—trachea, main stem, and lobar bronchi—due to intraluminal benign or malignant lesions. Laser therapy may provide palliative relief in an asphyxiating patient for whom no therapeutic alternative previously existed.

The electromagnetic or photon energy of lasers is absorbed by tissues and dissipated as heat-causing destruction. In the case of the neodymium-YAG laser, energy is transmitted through a thin, flexible quartz fiber that easily passes through the biopsy channel of a flexible or rigid bronchoscope. The procedure is done in an operating department or its equivalent under full anesthetic control, preferably through a ventilating rigid bronchoscope, and generally requires less than two hours of operating time and two days' stay in a hospital.

Those intraluminal lesions that are most technically responsive are short, polypoid, and only partially obstruct a major airway. Alternatively, extensive or predominantly peribronchial (extraluminal) lesions as detected by bronchoscopy and chest computed tomography are not easily palliated.

Most symptomatic patients who require laser treatment have primary or metastatic lung cancer that has recurred or cannot be controlled despite previous or concurrent surgical therapy, radiation therapy, or chemotherapy. In selected cases, however, patients having severe dyspnea, wheezing,

stridor, cough, hemoptysis, or unresolved pneumonia or atelectasis may require immediate initial laser treatment because of life-threatening symptoms associated with a benign or malignant lesion in a major airway. Symptomatic relief from asphyxiation in a patient with endobronchial malignancy can be achieved for an average of six months.

Laser therapy is clinically justified for the initial treatment of benign tracheal stenosis due to an outgrowth of a fibrous web or diaphragm in symptomatic patients with severe air flow limitation who have not responded to mechanical dilatation. It can offer excellent palliative relief and in some cases be curative. Optimal results may ultimately require additional surgical resection or a Montgomery tube. Tracheomalacia is not an indication for laser therapy.

We have been impressed with the frequent incidence of malignant or benign lesions of the trachea or main-stem bronchi (or both) in symptomatic patients that go undetected by chest roentgenograms. Chest computed tomography, pulmonary function studies, and bronchoscopy may be necessary in unresolved cases. Current research for the detection of unsuspected endobronchial malignant tumors involves fluorescence imaging using injected hematoporphyrin derivative and krypton ion laser. In addition, photodynamic ablation therapy may be achieved by using an argon-pumped dye laser causing irreversible tissue oxidation.

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Lung Transplantation

NINE YEARS AFTER LUNG TRANSPLANTATION was shown to be feasible in dogs, the first human lung transplantation was done in 1963. In the next two decades, rapid developments in the field of solid organ transplantation took place, but the feasibility of lung transplantation was held back by difficulties with immunosuppression, bronchial healing, and infection. In spite of that, in the mid-1980s successful lung transplantation in humans became a reality in Toronto, Canada, where the first procedure was carried out. Since that time several centers have begun doing both single- and double-lung transplants with excellent results. It is now possible to offer lung transplantation in appropriately selected and treated candidates with a 60% to 70% one-year survival figure. There are several four-, five- and six-year survivors in the lung transplantation program from Toronto. The availability of more selective and powerful immunosuppressive agents including cyclosporine, OKT3, and other monoclonal antibodies is now making appropriate and selective immunosuppression possible. A better understanding of posttransplantation infection with advances in the diagnostic techniques has led to the rapid recognition of these infections and their treatment, leading to better results.

Current indications for single-lung transplantation vary slightly from center to center. At the moment, common indications for single-lung transplantation include pulmonary fibrosis, pulmonary emphysema from whatever cause, Eisenmenger's syndrome with simple intracardiac defects, and primary pulmonary hypertension. Double-lung transplantation is indicated in patients who have end-stage bilateral septic disease and thus require replacement of both lungs to prevent postoperative infection. Such diseases as cystic fibrosis and bronchiectasis are common indications of double-lung transplantation in 1990. The criteria for acceptance into the program include an appropriate psychosocial history and a lack of severe diseases in other organ systems.

Lung transplantation offers several advantages over heart-lung transplantation, but most particularly offers a feasibility of donation that does not occur with the more common and more established heart-lung transplantation. The organ allocation system in the United States provides that when a patient is on the waiting list for a status I heart, the organ will be allocated to that recipient. Because of this, there are frequently hearts donated with the lungs not being used, if only heart-lung recipients are being screened. When a lung transplant patient is on the waiting list, however, the lungs are then usable for that patient. It is possible to obtain from a single donor two single-lung transplant preparations and a heart transplant for a third patient. This has been carried out in several centers throughout the world.

At a recent seminar on lung transplantation, it became apparent that more than 200 lung transplantations have been done worldwide in the past year or two with the survival figures as mentioned. It is obvious that this is no longer an experimental procedure but one that is a therapeutic necessity in many patients who are otherwise condemned. In the future, we will see the indications widen and the procedure being done in many centers in much the same way as the clinical activity in heart and liver transplantation has changed in the past ten years.

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Transtracheal Oxygen Therapy

GIVING SUPPLEMENTAL OXYGEN has been shown to improve survival in persons with chronic obstructive pulmonary disease (COPD) who have significant hypoxemia. In the National Institutes of Health Nocturnal Oxygen Therapy Trial, patients with a Pao_2 of 55 mm of mercury or less (oxygen saturation $\leq$ 88%) when stable or a Pao_2 of 56 to 59 mm of mercury (oxygen saturation of 89%) in association with polycythemia or cor pulmonale were randomly assigned to receive either nocturnal oxygen or continuous oxygen therapy. Those advised to use oxygen continuously actually used it an average of 19 hours per day and lived considerably longer than those using oxygen only at night. Oxygen therapy can also enhance the exercise capacity in persons with hypoxemia.

Administering oxygen through a nasal cannula (nasal prongs) has been the conventional mode of delivery in outpatients, but the delivery of oxygen through a transtracheal catheter was reported almost a decade ago. Initial concerns that transtracheal catheters would commonly become infected and cause chronic irritation have not been confirmed. The advantages of the transtracheal administration of oxygen over that of a nasal cannula include eliminating

the irritation of the nose and ears from the nasal prongs and tubing, being able to instill a saline solution through the catheter to help liquefy thick secretions, being able to reduce the flow rate required to maintain a satisfactory blood oxygen level to half or a third of that using a nasal cannula, and eliminating the obviously visible nasal cannula. The reduced quantity of oxygen needed allows patients to use smaller portable oxygen systems, enhancing the ease of mobility. Patients with transtracheal catheters are more likely to receive the recommended amount of oxygen at night, as the oxygen connection to the catheter is much less likely to become displaced than is a nasal cannula.

Possible concerns with regard to the use of transtracheal catheters for administering oxygen are that it requires a physician trained in the technique of catheter placement; it is more expensive than a nasal cannula to introduce initially and to replace; it requires some skill on the part of patients and their families to clean and maintain; and it is prone to the attachment of mucous plugs to the catheter, which can provoke coughing and cause airway obstruction.

Most patients who have compared the two routes of administration clearly prefer the transtracheal catheter to a nasal cannula for continuous oxygen therapy. As more physicians become experienced in placing these catheters, this mode of oxygen delivery will likely become much more common.

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Pharmacologic Management for Stopping Cigarette Smoking

All pharmacologic interventions for stopping cigarette smoking are thought to work by diminishing nicotine withdrawal symptoms after the patient stops cigarette use. There is no "magic bullet" that will make a patient stop smoking. All medications available, both those proved effective and those that are experimental, require a patient motivated to stop smoking and a physician motivated to assist the patient.

Nicotine replacement therapy remains the cornerstone of pharmacologic management. The only practical way of providing nicotine replacement currently is through the use of nicotine polacrilex (Nicorette). Numerous published studies show that nicotine replacement therapy using this medication can produce significant abstinence results, not only at the end of treatment (73% versus 42%) but one to two years after treatment began (44% versus 12%). Such results can only be achieved as part of a planned, professionally supervised program. Physician prescription cannot simply be phoned in; rather, the prescription must include the proper instruction in medication use and professional follow-up. Otherwise, nicotine replacement therapy is ineffective.

A critical step for achieving effective results with nicotine replacement therapy is providing patients with proper and complete instructions for medication use. Patients should anticipate using medication for three to six months. If they smoke a pack a day, they should use 12 pieces of nicotine polacrilex a day; if a pack and a half, 16 pieces a day; and, if two packs, 20 pieces a day. The medication should be tapered off slowly over two to four months. Patients should understand that nicotine polacrilex cannot be used while drinking beverages such as tea, coffee, soft drinks, milk, or alcohol, as the acid pH of these beverages completely blocks the release of nicotine from the medication. Present data show that the nicotine replacement therapy works synergistically with behavioral interventions and will boost the effectiveness of the behavioral intervention twofold to threefold. This conclusion applies whether the behavioral intervention is simply a physician advising a patient to stop smoking or intensive behavior modification.

Several new technologies for delivering nicotine—transdermal patch and nasal spray—are undergoing clinical testing, with initial, promising results for the patch at the end of a three-month treatment period. Other, totally different pharmacologic interventions are in early clinical testing. Trials of the use of clonidine hydrochloride (Catapres) and of doxepin hydrochloride (Sinequan) have shown excellent and significant results at the end of a four-week treatment period. Results in women using clonidine versus placebo tablets at the end of four weeks' treatment were excellent (72% versus 15%), but results in men were disappointing (47% versus 50%). A second clonidine study, however, failed to replicate those results, finding no difference in either abstinence rates or withdrawal symptoms. Clinical trials with adrenocorticotropic hormone (ACTH) and fluoxetine are underway. The use of clonidine, doxepin, ACTH, and fluoxetine must be regarded as experimental at this time. Agents that may prove useful in the future include central nicotinic receptor blockers, excitatory amino acids, serotonin (5-hydroxytryptamine)-receptor antagonists, and calcium channel blockers.

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Ventilator Use in the Inpatient Management of Chronic Obstructive Pulmonary Disease

Mechanical ventilation in patients with chronic obstructive pulmonary disease is indicated when conservative measures such as the treatment of precipitating causes, the administration of oxygen, the removal of secretions, and bronchodilator therapy have failed. Clinical signs suggestive of respiratory failure include tachypnea—respiratory rate more than 30 breaths per minute—prominent accessory respiratory muscle use, and asynchronous motion of the thorax and abdomen during inspiration. This has been called thoracoabdominal paradox and is seen when the respiratory muscles are working excessively against high loads. The severity of the respiratory failure can be evaluated by measuring arterial blood gas values. Hypoxemia can

be managed by giving supplemental oxygen. The major criterion for ventilatory support is the severity of acute respiratory acidosis. Generally if the pH falls below 7.25, mechanical ventilation is indicated. Hypercapnia with a compensated acidotic base state—pH 7.4—is not an indication for mechanical ventilation.

The major goals of ventilation are to provide adequate gas exchange while the precipitating cause of the respiratory failure can be managed. Many authorities now recommend that ventilatory support should also aim to rest the ventilatory muscles. The basis for this suggestion is that fatigue of the respiratory muscles is considered a complicating factor in the pathogenesis of respiratory failure. Recovery from the acute episode and facilitation of weaning may depend on providing adequate rest to the respiratory muscles. This thinking has influenced the modes of ventilation now in use.

Until recently, the major modes of ventilation available consisted of control, assist-control, and intermittent mandatory ventilation. The original promise of intermittent mandatory ventilation to improve patient ventilator synchrony and prevent the development of posthypercapnic metabolic alkalosis during ventilation has not been realized. Furthermore, it has not been shown to be superior in weaning patients from mechanical ventilation. Assist-control ventilation provides only partial rest to the respiratory muscles. If the respiratory drive is high, considerable work is expended by a patient.

Pressure support ventilation is a new mode of ventilation whereby a constant airway pressure is applied to the airway during spontaneous breathing or while using the intermittent mandatory ventilation mode. The patient is able to control tidal volume and inspiratory flow rates. The higher the level of pressure support applied, the larger the tidal volume and minute ventilation and the greater the reduction in patient energy expenditure. Low levels of pressure support—4 to 8 cm of water—are considered helpful in overcoming the resistance of artificial airways and ventilator circuits. When these levels of pressure support are used in intubated patients during spontaneously initiated breaths, it may be easier to evaluate the patient's ability to sustain spontaneous ventilation after extubation. Ongoing research will clarify the role of pressure support in improving patient ventilator synchrony, alleviating respiratory muscle fatigue, and facilitating weaning.

Once mechanical ventilation is started, the initial ventilator settings, rate, and tidal volume should be adjusted to maintain a normal pH. In cases of acute hypercapnia, carbon dioxide levels can be reduced rapidly to baseline to normalize the pH. In patients with chronic respiratory acidosis—a rapid reduction in the $Paco_2$ will cause an acute respiratory alkalosis superimposed on the present acid-base state and should be avoided. In this state, seizures and death can occur. Patients should be "reset" at their maintained $Paco_2$ before being weaned from the ventilator.

Higher inspiratory flow rates decrease inspiratory muscle work, reduce the physiologic dead space, improve arterial oxygen tension, and provide increased exhalation time and therefore a reduction in intrinsic positive end-expiratory pressure (PEEP). Intrinsic PEEP occurs with airway obstruction, delayed exhalation, and a consequent increase in the functional residual capacity. Successive breaths arrive prematurely before the previous expiration is complete, and intrathoracic pressure does not return to atmospheric levels, remaining persistently elevated, as when external PEEP is applied. Intrinsic PEEP is exceedingly common in patients with obstructive airways disease. Under normal circumstances, the pressure gauge on the ventilator records atmospheric pressure during expiration and reads zero even in the presence of high levels of intrinsic PEEP. The level of intrinsic PEEP can be measured by occluding the expiratory valve at the end of exhalation and noting the pressure on the ventilator gauge before the next inhalation. Intrinsic PEEP also causes distortion of the measurement of central venous pressure and lung compliance.

The mortality of chronic obstructive pulmonary disease in patients who require mechanical ventilation for acute respiratory failure ranges from 21% to 42%. About 3% of those who survive require long-term mechanical ventilation.

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Pulmonary Disorders Caused by Illicit Drug Use

ILLICIT DRUGS may be administered intravenously, intranasally, orally, or through inhalation by smoking. Pulmonary disorders associated with the intravenous and intranasal abuse of drugs have been well documented. Recent attention has focused on the effects of inhaling these drugs. There have been a number of recent reports of pulmonary disorders attributed to the inhalation of marijuana, cocaine, and methamphetamines.

Inhaling marijuana smoke may result in injury to the conducting airways as a result of noxious gases, oxidants, and other toxins in the particulate phase. Pathologic effects include ciliary dysfunction, inflammation of airway walls, squamous cell metaplasia, and peribronchial fibrosis. The large number of toxic substances produced during pyrolysis is similar to that produced during cigarette smoking. The physiologic effects of habitual abuse include increased airway resistance, ventilation-perfusion abnormalities, and decreased gas exchange surface, resulting in symptoms of cough, dyspnea, wheezing, and diminished exercise tolerance. The concentrations of some carcinogens and other toxins are greater in marijuana smoke than with tobacco, which may place regular marijuana users at a higher risk for bronchogenic carcinoma.

Cocaine hydrochloride must be converted to the pure alkaloid form ("crack") before it can be heated, volatilized, and inhaled. Abusers may have chronic cough, dyspnea, acute pulmonary hemorrhage, or, rarely, pulmonary edema. Patients may present with acute bronchospasm indistinguishable from an acute asthmatic attack from other causes. A decrease in the diffusing capacity of the lung for carbon monoxide (D_Lco) is the most commonly cited physiologic abnormality. The underlying mechanisms of decreased D_Lco from cocaine use are not well understood. Long-term cocaine smoking may cause a syndrome of fever, cough, and radiographic findings of diffuse pulmonary infiltrates. The pathophysiology of this clinical syndrome is postulated to be either from the direct action of cocaine or from volatile hydrocarbons. Dyspnea may also be a result of a pneumothorax caused by smoking cocaine and is thought to be due to the Valsalva's maneuver commonly practiced by these smokers.

Methamphetamine hydrochloride must first be highly purified to have the volatility necessary for inhalation. The purified form has a crystalline appearance and is commonly called "ice." This inhalation drug problem is epidemic in Hawaii and on the West Coast. The data on pulmonary complications, both acute and chronic, are limited. Physiologically, methamphetamine is a direct central nervous system stimulant that also increases sympathetic nervous system activity and serum catecholamine concentrations. Smoking "ice" results in central nervous system symptoms of euphoria, agitation, and psychosis and cardiovascular symptoms of hypertension, tachycardia, and arrhythmias. Although a direct effect of methamphetamine on lung tissue has not yet been proved, acute dyspnea and cough are associated. Because smoking "ice" is a relatively new phenomenon, it is possible that some yet-undescribed pulmonary or radiographic finding may occur.

In patients with unexplained cough, dyspnea, or radiographic findings, clinicians should consider illicit drug abuse. A urine immunoassay can detect cocaine or methamphetamine metabolites as long as two days after use.

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Mechanical Respiratory Support at Home

LONG-TERM HOME VENTILATOR SUPPORT is an attractive option for many patients with severe stable respiratory failure due to a variety of neuromuscular, musculoskeletal, and pulmonary diseases. Guidelines and standards now have established reasonable indications, selection criteria, protocols, and the team approach needed to prepare for home care and for follow-up.

When ventilator support is initiated electively, patients are able to adjust more easily, with assistance from trained family members. Elective ventilator support is usually needed less than 12 hours a day. Although tracheostomy has been used frequently, noninvasive methods should be considered first, such as positive pressure ventilation using a nasal mask or mouthpiece; negative pressure ventilation using a cuirass, iron lung, or various other techniques; and a rocking bed. Recent experience with the nasal mask suggests its advantages in effectiveness and in avoiding upper airways obstruction. The cost involved in ventilator assistance on an elective basis is within reach of usual resources for many patients, about $20 to $40 a day.

In contrast, patients in intensive care units on discharge require long-term ventilator support, usually 12 to 24 hours a day. A tracheostomy is often needed both for ventilation and to remove secretions. Patients may have multiple impairments and limited functional performance. Because more complex care is required, patients are more often dependent on others for most of the 24 hours. Paid caregivers are generally required to assist the family. The financial costs—about $150 to $300 a day—are greater than most patients can arrange, unless third-party or public funds are available, but are still less than the costs for hospital care. Adjusting to the unexpected and catastrophic situation is difficult for patients and families.

Hospital discharge preparation is a multidisciplinary team process that can enable most of these patients to go home or to another community alternative site. Experienced medical centers can assure a quality of care in the home environment that is comparable to that in a hospital. Two-year survival can be more than 70% for patients with neuromuscular disorders and more than 50% for patients with chronic obstructive pulmonary disease. Care must be coordinated with community agencies, a medical equipment company, and emergency services including the utility company, fire department, and a hospital emergency department. Patients generally prefer their quality of life at home when compared with the hospital setting; they can live in ways that are more personally satisfying and socially useful.

The challenges and burdens for a patient's family and the community home care resources can be enormous, particularly when care is complex and carried on for several years. The funding and community services required for these patients and their families need to be improved. Properly planned, however, long-term home respiratory support can be rewarding for patients, their families, and the medical team directing care.

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Inhaled Pentamidine Therapy for *Pneumocystis carinii* Pneumonia

INHALED PENTAMIDINE THERAPY is now indicated for the primary and secondary prophylaxis of *Pneumocystis carinii* pneumonia in patients with human immunodeficiency virus infection. Both primary prophylaxis, for persons with fewer than 2×10^6 per liter (200 per μl) CD4 (helper) lymphocytes who have not had an episode of *P carinii* pneumonia, and secondary prophylaxis, for those patients who have had a previous episode of the disease, are administered through a Respirgard II jet nebulizer (Marquest, Englewood, Colorado) at a dose of 300 mg of pentamidine isethionate once a month. This regimen is the result of a recent study of inhaled pentamidine as secondary prophylaxis for *P carinii* pneumonia that found giving 300 mg once a month superior to 30 mg or 150 mg given every two weeks. Relapse rates at 18 months were approximately 10% in patients receiving 300 mg once a month compared with a 65% relapse rate at one year in historical controls.

Toxicity from inhaled pentamidine has been minimal and limited to bronchospasm, preventable with the previous administration of inhaled bronchodilators.

Relapses of *P carinii* pneumonia after inhaled pentamidine therapy tend to occur in the apices of the lungs and possibly are related to poor drug deposition in those areas. Spontaneous pneumothorax (probably due to rupture of pneumatoceles in the apices) and extrapulmonary pneumocystosis have been reported in patients receiving inhaled pentamidine, raising a concern that pneumocystosis is in fact a systemic process and not one localized to the lung. Therefore, a combination of parenteral and local (inhaled) prophylaxis may be required. Two ongoing prophylaxis tri-

als will further define the use of inhaled pentamidine. One compares using 300 mg with 600 mg of inhaled pentamidine once a month and the other compares using inhaled pentamidine, 300 mg once a month, with using the combination drug, trimethoprim and sulfamethoxazole, one double-strength tablet twice a day, or dapsone, 50 mg twice a day.

Studies are also in progress comparing the use of inhaled pentamidine with that of trimethoprim-sulfamethoxazole for the treatment of mild to moderate *P carinii* pneumonia. Standard therapy for this disease in patients with the acquired immunodeficiency syndrome has consisted of trimethoprim-sulfamethoxazole (as 15 mg per kg per day of the trimethoprim component in three to four divided doses given orally or intravenously) or of pentamidine isethionate (4 mg per kg per day as a single intravenous infusion). Unfortunately, both of these regimens are associated with substantial toxic reactions, and as many as 50% of patients will require a change or modification of therapy because of toxicity. Nausea, vomiting, fever, rash, neutropenia, and elevated aminotransferase levels occur with the use of trimethoprim-sulfamethoxazole. Parenteral pentamidine use is associated with hypotension, hypoglycemia, azotemia, pancreatitis, and neutropenia. Alternatively, inhaled pentamidine therapy has not been associated with significant systemic toxicity.

These observations led to a trial of inhaled pentamidine, 600 mg per day for 21 days, as sole therapy in 15 patients with *P carinii* pneumonia. Of 15 patients, 13 completed treatment and 14 patients survived an admission to hospital. A patient who had concomitant disseminated tuberculosis died during the second week of therapy. This encouraging study resulted in a comparative trial of inhaled pentamidine, 600 mg a day, and trimethoprim-sulfamethoxazole, 15 mg per kg a day of the trimethoprim component, in approximately 250 patients. Patients were treated for 21 days in a randomized, double-blind manner. Findings from this study are pending the analysis of data. Until then, inhaled pentamidine as therapy for *P carinii* pneumonia should be considered experimental.

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Editorials

Sailing Out of the Doldrums

It is hard to sail in the doldrums. The weather is scorching. Winds are baffling. Fitful squalls become paralyzing calms. It is best to sail determinedly out of the doldrums or to avoid sailing into them. For our purposes, then, it is unwise to dwell on the many doldrums swamping our profession: exhaustion, disappointments, paperwork, accusations, loss of collegiality, diminished stature. Not long ago, some medical sailors resolved to focus on the good news, if only for a few moments. They noted that while it is fashionable to complain, fashion can be constricting. They set out to review and relish some of the elements of our profession that hearten them, even now. They mentioned:

- The march of biomedical science: Never have physicians been able to do so much for so many.
- The privileges and pleasures of the doctor/patient relationship: Physicians are part of the parade of life, never bystanders.
- The challenges of difficult diagnoses and treatments, even AIDS.
- The opportunities to learn from patients and about patients; the opportunities to learn about life, about courage, about applying science.
- The pleasures of preventing disease and disability and, of course, of returning patients to health.
- The satisfactions of being a patient's advocate, of being a trusted ally, of being recognized as well informed.
- The thrill of perfecting a new technique or making a difficult diagnosis.
- The remarkable variety and number of choices:

Career tracks: Patient care, research, teaching, administration, health policy, combinations thereof.

Time management: Full-time, part-time; shared practices; sabbaticals.

Locales: Fields and streams, inner cities.

The ever-broadening scope of medicine: Geriatrics, adolescent medicine, space medicine, medical informatics, imaging, lasers, transplantation, infertility, nutrition.

One physician said, "Consider the alternatives. There is not much else available if you want to do something worthwhile for people." Another noted, "Where there is chaos, there is opportunity." One smiled and said, "I like it when they call me 'Doc.'"

Doldrums recede in the refreshing breezes of renewal.

LHC

Ignorance—Inevitable but Invigorating

In this issue Marlys and Charles Witte and Dennis Way have written a fascinating article.[1] At times the prose takes on an almost Joycean, free-association quality, and we are obliged to stay alert to track through the syntactic labyrinth. The essence of the article is epitomized by this statement: "Thus, some of our best students, by dint of hard work, probing intellect, and resourcefulness, are leaving the University of Arizona College of Medicine more ignorant than they entered!" I loved it!

To dramatize their "pursuit of ignorance," the authors selected several patients with lymphatic obstructive disorders to highlight the remarkable lack of knowledge that pervades any pathophysiologic discussion of this still enigmatic major drainage system of the body. Certainly ignorance abounds here. But they could have selected almost any other system. For example, the psychoneuroimmunological messages that fly thick as arrows between mind and body remain a great mystery. But no generation in medicine has been more humbled by exploding knowledge than ours.

In selecting the lymphatic system (they include lymphocytes, lymph nodes, lymph channels, and lymph fluid) as their exemplar, the authors picked a most appropriately baffling subject. The linkage between blocked lymphatics and lymphangiogenesis and angiogenesis fascinates the authors, and with good reason. The ability of the body to generate vessels for new tissue, albeit fat, muscle, or regenerating scar, on demand and with astonishing rapidity is a continuing mystery. If a person gorges and gains 10 lb in a week, the new fat is endowed miraculously with afferent and efferent vessels, plus lymphatics, nerves, and so forth. Is there an "angiogenic cytokine"?

This remarkable, thin-walled, fragile vascular system is entrusted with awesome responsibility—to return interstitial fluid to the venous side. The fearsome clinical consequences of its perturbations are the stuff of horror pictures in classic textbooks (for example, filaria-invoked elephantiasis). The authors provide some lurid pictures. So, although we have known about it for a long time, there remains little that can be done to repair a badly disordered lymphatic system.

I suspect it is appropriate to include lymphocytes in the consideration of the "system." When I left the academic cloister, the lympocyte was still just a strange, round, peripheral blood cell with a large azurophilic nucleus; no one knew much about it. In infectious mononucleosis (pre-Epstein-Barr), we knew the nucleus got dented, and some peculiar inclusions showed up in the cytoplasm. In patients with acute lymphoblastic leukemia, we saw a horrendous outpouring of primitive precursors that crowded out the marrow. And in those with chronic lymphocytic leukemia, an outrageous productivity of mature cells clogged up nodes and even obstructed lymphatics. But we had no hint of all the wonderment that was to follow as MacFarlane Burnett, Bob Goode, and other pioneers began to unravel the mysteries of the immune system. How far we have come!

Each new level of comprehension opens up new vistas of ignorance. As the authors indicate, the whole area of immunology and molecular biology reminds us of a vast, coiled-up tapestry that has just begun to unfurl. But instead of unrolling in an orderly fashion, it has unfolded and proliferated simultaneously, if erratically, in all directions. Discoveries in every section link up with those adjacent or even leap over each other to join remote areas with some rare and remarkable synergies. It is fast becoming a crazy quilt with junctions and cul de sacs and parallel channels. AIDS, the terrible, has been the unlikely catalyst.

One of the patients described by the authors had the acquired immunodeficiency syndrome. Of course, it was unrecognized back in 1968, but the authors were sufficiently intrigued by the unfamiliar clutter of disparate and disturbing signs, symptoms, and laboratory events that they preserved the tissue and ultimately established human immunodeficiency virus positivity. Their cases serve to illustrate the ultimate illumination—if one is aware of ignorance and perseveres in the pursuit of knowledge.

Ignorance is not bliss. It is the source of many terrible afflictions: prejudice, fear, cruelty, and wars. The fundamental problem with the true ignoramuses is that they do not know that they are ignorant; it is a classic "catch 22."

They who are ignorant and do not know they are ignorant are doomed to perpetual ignorance, unless enlightenment comes from some external source. That stimulus is education. The appreciation of ignorance is the first step to wisdom. The greater the knowledge, the greater the appreciation of the ignorance. This is the wisdom that is offered to Arizona medical students.

The dawning realization that we lack knowledge in a given area can precipitate several actions. Most people experience an initial sense of exhilaration—almost a revelation—and are stimulated to cast the light of intellect into the dark corners. Others are embarrassed, perhaps even intimidated by the new knowledge, and tend to ignore and reject it. They retreat into the comforting shadows of deadening ignorance—intellectual troglodytes.

I suspect the other face of ignorance in medicine is arrogance. I can still recall studying for the American Board of Internal Medicine's written and oral examinations. I hit the books an average of four hours a day for about a year. I had acquired a 5-ft file of "hot articles"—reprints and clipped original editorials from *New England Journal of Medicine, Journal of the American Medical Association, Annals of Internal Medicine, Archives of Internal Medicine, American Journal of Medicine,* plus every key article from the past three years. One week before the examination I could reach into that file, pluck any article at random, read the title, and recite the key teaching point(s)—and give a small lecture on the subject. I exuded hubris. There was nothing worth knowing that I did not know about internal medicine. (I believed that if I had failed that examination, I would have decompensated.)

I happened to wander through that pile ten years later. I would estimate that 90% of the information it contained was either hopelessly out of date or downright incorrect. So much for knowledge; make way for ignorance. Yesterday's absolute truth is today's tiresome anachronism. The treadmill never stops running; if you slow down or stop, you move backwards.

The article tickled another thought. I think we have all learned another lesson over the past 30 years. The era of the Herr Geheimrat has passed. He (there were few women) represented the ultimate unimpeachable authority. Enclosed in a kiosk of towering isolation—insulated from criticism by the suffocating cultural structure of the system—he sailed majestically through the wards at the head of a white-coated flotilla of docile supplicants. He pontificated without fear of challenge, much less contradiction. It was a structure designed to institutionalize ignorance and frustrate any attempt at innovation.

It all came apart in the wake of World War II, when the medical knowledge explosion made it impossible (if not ludicrous) to assume that any single person could be the unassailable repository of all clinical knowledge. The system died harder in Europe than in the United States, but the inevitable divvying up of knowledge into specialties, subspecialties, and subsubspecialties was its death knell. Open teaching rounds with dialogue between chief and staff and with the encouragement of challenge and debate were the great American contribution to medical education.

The essay by Witte and co-workers is a gem of good writing and provocative thinking. Some of it is tongue-in-cheek, but their arrow hits the target. The metaphoric lymphatics remain mysterious, even in our current state of "escalating enlightenment," but at least we know we are ignorant.

Next I wish they would find out why it feels so much better to cross one's legs when sitting for long periods, or what will happen when we dispatch crews to Mars and deprive them of old-friend gravity for three-plus years.

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Challenges From the Environment

THE DECADE JUST BEGUN could surely be called "the Decade of the Environment." The challenge of pollution-related illness faces us at this moment. Recognizing environmentally associated diseases and treating them effectively are clinical problems whose solutions will need increasing attention for years to come. Depletion of the ozone layer, acid rain, the "greenhouse effect," and ionizing radiation from nuclear energy plants represent problems that are global in scope yet rarely, if ever, noticeably affect individual medical practices. On the other hand, industrial chemical pollution, the "sick building syndrome," and toxic wastes are more localized issues, affecting circumscribed occupational or residential communities. They are examples of the types of problems that now confront the ordinary physician.

In this issue of the *Journal,* Sparks and co-workers report on their investigation of 53 employees of a large aircraft manufacturing company.[1] A physician previously diagnosed these workers as suffering from a "new" disease called the "aerospace syndrome." When examined by a team of experts from various specialties, however, it was discovered that the workers as a group had a condition characterized by anxiety and depression that was not relieved when they left the workplace. They experienced multiple somatic symptoms without evidence of physical illness, so that the authors report them to be "partial somatizers."

The so-called aerospace syndrome apparently fits well into the category of illness previously referred to as "multiple chemical sensitivities."[2] The latter term describes persons who report multiple symptoms when they are exposed to a variety of common substances, such as perfumes, automobile exhaust fumes, household cleaning products, and new clothes. Many of these "chemically sensitive" persons report adverse reactions to several foods and drugs. No diagnostic physical finding or laboratory test characterizes their condition. In many cases the problem seems to be initiated by a known or suspected occupational or environmental chemical exposure. Those who have investigated this problem sharply disagree regarding its cause. Some view the illness as a form of chemical immunotoxicity.[3] Others see the problem as a somatization disorder[4,5] and others as an iatrogenic condition.

The evaluation of the aerospace syndrome reported by Sparks and associates has some definite shortcomings, but it lends support to the concept that psychological origins often can explain multiple symptoms occurring with exposure to low levels of environmental chemicals if the patient's symptoms are not consistent with known toxic properties of the chemical. The authors point out that the employees in this case were using chemicals found widely in modern-day industry. The ambient levels of chemicals in the factory were low. It should be noted, however, that these measurements were made well after the employees first became symptomatic, so it is possible that their exposures to some of these chemicals may have been higher in the past. In fact, some of the workers reported contact dermatitis and mu-

cous membrane irritation that later resolved with the cessation of exposure. The study also lacks an appropriate control population. Investigation of those workers who had the same exposure but did not file complaints of illness would have strengthened the conclusions.

The authors are to be congratulated for carrying out their study under restrictive conditions that limited them from obtaining the data that would have made the investigation ideal. Whenever environmental pollution or workplace safety appears to be a factor in disease, the case is likely to enter the political arena and the courts. Political and legal decisions in matters of health and disease are only as good as the scientific data on which these decisions are based. Therein lies a dilemma for the clinical investigator. Research into occupational and environmental diseases frequently involves epidemiologic methods. A proper investigation of occupational disease is virtually impossible to design and carry out in the face of impending litigation and in an atmosphere of intense media coverage. It is difficult to enroll the control subjects needed for a well-designed study under such circumstances. Both employers and employees have vested interests in the results, and these interests usually conflict. A controlled exposure of subjects in a laboratory to a suspected chemical is often required for a definitive study, but all too often a definitive procedure like this must be rejected because of the specter of liability.

The study reported by Sparks and colleagues raises a second issue—that of laboratory credibility. The workers in this case allegedly had antibodies to formaldehyde, reported by a commercial laboratory that performed blood tests on the workers. When retested in a university medical center research laboratory where the formaldehyde antibody test had originally been developed, the results were negative. Physicians who evaluate and treat occupational illness are approached by certain commercial laboratories offering a variety of tests, including measurements of antibodies to chemicals, lymphocyte surface markers, and blood and urine levels of industrial chemicals, pesticides, and other potentially toxic products. The validity of many of these measurements and the true "normal" ranges are defined poorly, if at all. Yet such tests are being used to diagnose occupational disease.

The present study raises another issue. How do we define a disease or syndrome? Ideally, a disease is defined on the basis of etiology and pathophysiology. Too often, however, patients present to their physicians with complaints and findings for which there is no clear cause or pathogenesis. In the case of the acquired immunodeficiency syndrome (AIDS), a working case definition was set up by a group of experts to define the diagnosis until the causative virus was isolated; today an etiologic diagnosis of human immunodeficiency virus infection is straightforward.

The term "aerospace syndrome" was created by the media because a physician was convinced that a group of commercial aircraft workers suffered a new disease of toxic origin. The naming of a new syndrome in this case was clearly premature, and even the name was inappropriate. It remains to be seen how long this new name will persist. The term "multiple chemical sensitivities" implies both cause and pathogenesis, neither of which is yet supported by any hard data. Nevertheless, these names carry symbolic meaning to patients. Such names could well contribute to a perception of disability that might not be warranted.

The problem of low-level chemical environmental exposure as a cause of illness to an individual, to the work force, and to the community challenges all in medicine. Too few medical investigators, however, have taken up the challenge. No one will disagree that we live today with human-made pollution. No one will dispute the desirability of a clean environment for reasons of good health and aesthetics. Many diseases that are caused by toxic and microbiologic contaminants in the air, food, and water have been described and studied with rigorous scientific methods. Many physicians active in the field of environmental and occupational medicine, however, find the increasing tendency today to attribute almost any illness or symptom to an environmental toxin without adequate study a disturbing one. There is every reason to think that the problem will get worse. As industry creates and supplies new products that enhance the quality and safety of daily living, workers, consumers, and the general public will be increasingly at risk of exposure to potentially hazardous substances. The present case is a good example. These aircraft workers were involved in the manufacture of a product for making airline travel safer.

The policymakers who must decide how best to maintain a clean environment for the public good need high-quality input from the medical profession. Full cooperation must be effected among the physicians who carry out studies of industrial pollution, the population at risk, their representatives (unions and legislatures), industry, and the judicial system. A litigious society makes this type of cooperation exceedingly difficult. But it is not impossible.

Clearly, physicians must provide leadership by coming up with innovative proposals for pooling the resources of industrial management, unions, and clinical science. This process would in no way restrict a person's right to be compensated for injury or illness caused by someone else's wrongdoing or by occupational illness. We cannot ignore environmental pollution without risking unnecessary disease. Neither can we ignore the basic principles of good medical practice and sound research, subject patients to unsubstantiated diagnosis, and mislead the media without risking unnecessary psychological harm and disability in the work force.

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Endometrial Cancer—The High-Risk Early-Stage Patient

THE ARTICLE by Fu and co-workers is a comprehensive synopsis of the endometrial cancer problem, touching most of the recent developments in the areas of histogenesis, diagnosis, treatment, and prognosis.[1] I have selected several points in the review to emphasize and enlarge upon.

Although the authors did not use the more current terminology for endometrial hyperplasia (simple or complex with or without atypia), it remains true that the presence of atypia is the identifying feature of a premalignant lesion. Women in whom this form of hyperplasia develops should be managed by hysterectomy, health permitting, unless it occurs during the reproductive years. In most cases atypical hyperplasia, once manifest, is reversible by high-dose progestins but is incurable. Thus, the risk for cancer persists

for the life of the patient. Since overt cancer may coexist with atypical hyperplasia, the diagnosis of atypical hyperplasia must be based on the results of a formal curetting of the endometrium if nonsurgical therapy is contemplated. An intraoperative examination of the uterus will minimize the possibility of doing an inadequate operation if a cancer was missed at dilatation and curettage.

There are several common errors in the evaluation and management of women with endometrial cancer or symptoms thereof. As the article in this issue emphasizes, an endocervical curettage is a standard part of the endometrial biopsy or curettage done to rule out or diagnose endometrial cancer. The endocervical curettage has a dual purpose: to detect extension of the endometrial cancer into the cervix and to detect a primary cervical carcinoma. The treatment of these two conditions is quite different from that of endometrial cancer clinically confined to the corpus (stage I).

Postmenopausal bleeding is an extremely important sign that most women and physicians in our society recognize. A gynecologic examination is always indicated unless it is the routine, scheduled bleeding associated with cyclic hormone therapy. While cervical and vaginal cytologic examination is appropriate, it is not by itself an adequate evaluation. In the absence of an obvious vaginal or cervical bleeding source, endocervical curettage and endometrial biopsy must be done. Omitting the endocervical curettage can lead to a delay in the diagnosis of an endocervical cancer, dysplasia, or endocervical polyp, in addition to underestimating the extent of a primary uterine cancer.

In most situations surgical intervention is the first step in the treatment of endometrial cancer. With few exceptions the approach should be transabdominal through a vertical incision. Proper operative staging cannot be done through a low transverse incision. Careful, complete exploration of the abdomen and pelvis with documentation of the findings in the operative report is indispensable, given the proclivity this cancer has for lymph node and intra-abdominal metastases. Abnormal or suggestive nodes should be removed and a biopsy done of suspect peritoneal lesions. An intraoperative evaluation of the removed uterus by a pathologist will provide an accurate estimate of the degree of myometrial invasion, although on occasion a frozen section may be required. Since the risk of aortic node metastases is substantial in the presence of a grade 2 to grade 3 lesion with more than 50% myometrial invasion, a limited aortic node dissection is warranted. This procedure is beyond the scope of training for most gynecologists.

The difference in surgical skills required for a general gynecologic operation and a gynecologic cancer operation has led to the establishment of the subspecialty of gynecologic oncology. Most patients with uterine cancer requiring extended surgical therapy can be identified preoperatively and would benefit by having a gynecologic oncologist do the operation. The histologic grade is based, of course, on the findings of dilatation and curettage. Myometrial invasion can be determined with reasonable accuracy by means of a sonogram. In addition, the serum CA 125 level should be determined. An elevated value is a reliable indicator of metastatic disease. Management by a gynecologic oncologist is recommended if the CA 125 value is elevated or if the patient has a grade 2 to grade 3 cancer with more than 50% myometrial invasion, cervical extension, or evidence of metastases.

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Alerts, Notices, and Case Reports

Acute Delta Hepatitis During Treatment With Adenosine Arabinoside Monophosphate With Resolution of the HBsAg Carrier State

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HEPATITIS D VIRUS (HDV), a recently discovered human hepatitis virus,[1] is a defective RNA virus that requires concurrent infection with hepatitis B virus (HBV) for its replication.[2] Patients with concurrent HBV and HDV infections often have especially severe acute[3] or chronic[4,5] liver disease. Hepatitis D virus infection occurs worldwide, although it is rare in Asia. It spreads sporadically in the general population only in areas of high rates of carriage of the hepatitis B surface antigen (HBsAg), and, in areas of low HBsAg-carrier rates, infection develops only in persons at high risk for blood contact, such as drug addicts, homosexual men, and polytransfused hemophiliac persons.[6] Currently available data suggest that hepatitis D, or delta, virus superinfection of HBsAg carriers leads to chronic delta hepatitis 60% to 80% of the time.[7,8]

Experimental HDV infection of chimpanzees[2] and woodchucks[9] with chronic hepadnavirus infection has shown that the appearance of delta antigen in serum or liver leads to biochemical and histologic findings of acute hepatitis and a decrease in serum markers of hepadnavirus replication. Among the animals studied, one chimpanzee HBV carrier had the disappearance of HBsAg, and antibody to HBsAg (anti-HBs) developed during a nine-week follow-up period after acute delta infection.[2] In this report, we describe a patient with chronic, persistent hepatitis B in whom icteric acute delta hepatitis developed and who subsequently had the clearance of all markers of active HBV replication. We were fortunate to have complete serologic documentation of this because he was participating in a randomized trial of adenosine arabinoside monophosphate (ara-AMP, Warner, Lambert Laboratories, Ann Arbor, Michigan) at Stanford (California) University Medical Center.

(Garcia G, Smedile A, Bergmann KF, et al: Acute delta hepatitis during treatment with adenosine arabinoside monophosphate with resolution of the HBsAg carrier state. West J Med 1990 Jul; 153:80-82)

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Methods

Tests for HBsAg, anti-HBs, hepatitis B e antigen (HBeAg), antibody to HBeAg, antibody to the human immunodeficiency virus (HIV), and anti-delta were done with commercially available immunoassays (AusRia II, Ausab, HBeAg test, and anti-HIV and anti-delta enzyme immunoassays, Abbott Laboratories, North Chicago, Illinois). Dane particle-associated DNA polymerase activity (polymerase) was determined by the method of Robinson.[10] An HBV-DNA assay was done on 20 μl of serum using an HBV probe labeled with phosphate 32 and electroluted from a λ-vector in a slot-blot hybridization assay.[11] Routine liver function tests were done in the clinical chemistry laboratory at Stanford University. Interferon titers were measured in serum by a vesicular stomatitis plaque-reduction assay.[12] Hepatitis D virus RNA was assayed in serum RNA extracts by Northern blot hybridization with a ^{32}P-labeled cloned cDNA fragment of HDV RNA and expressed semiquantitatively on a visually graded scale of 0 to 4+.[13] Hepatitis D antigen (HDAg) was measured by an immunoblot assay using human serum positive for HDV antibody and *Staphylococcus aureus* protein A labeled with iodine 125 and expressed semiquantitatively on a scale of 0 to 4+.[14]

Liver biopsy specimens were examined in a blind manner by two of us (G.G. and P.B.G.). The biopsy specimens were graded with respect to architectural distribution, fibrosis, erosion of the limiting plate, and lobular activity using an arbitrary scale. The histologic diagnosis was established using the criteria of the Fogarty Diseases of the Liver and Biliary Tract International Committee.[15] Immunofluorescence for the delta antigen was done on formalin-fixed liver secretions as previously described.[1]

Report of a Case

The patient, a 29-year-old homosexual man with chronic persistent hepatitis B, was enrolled in a trial of adenosine arabinoside monophosphate in September 1982. He was an asymptomatic carrier of HBsAg, first discovered on routine screening in September of 1981. He said he did not use drugs parenterally and had no other risk for HBV infection. At trial entry the results of a physical examination were normal except for generalized lymphadenopathy; his HBsAg, HBeAg, anti-HIV, HBV-DNA, and DNA polymerase assays were positive; antibody to HBeAg was not detected. The patient has never had an opportunistic infection or tumor in the subsequent four years of follow-up.

The patient received ara-AMP, 2.5 mg per kg of body weight intramuscularly, twice a day during three 28-day periods beginning September 10, 1982, November 5, 1982, and January 1, 1983. On November 24, 1982, while receiving ara-AMP, he noted anorexia, epigastric discomfort, and constipation; jaundice was first evident on December 1, and the ara-AMP regimen was discontinued. Despite worsening jaundice, occasional nosebleeds, and progressive tender hepatomegaly for the next two weeks, he remained able to eat and drink fluids throughout his illness and had no neurologic or other hemostatic problems. On January 1, 1983, he complained only of minimal fatigue, and ara-AMP therapy was restarted. Fatigue and jaundice were no longer present on January 17, 1983.

The results of serum alanine aminotransferase (ALT) measurements and polymerase, HBsAg, anti-HBs, anti-delta, and HDV-RNA assays are shown in Figure 1. Hepati-

ABBREVIATIONS USED IN TEXT

ALT = alanine aminotransferase
anti-HBs = antibody to HBsAg
ara-AMP = code designation for adenosine arabinoside monophosphate
HBeAg = hepatitis B e antigen
HBsAg = hepatitis B surface antigen
HBV = hepatitis B virus
HDAg = hepatitis D antigen
HDV = hepatitis D virus
HIV = human immunodeficiency virus

tis D antigen was detected, along with a simultaneous decrease in polymerase activity, 12 and 10 days, respectively, before any symptomatic evidence of disease. The onset of symptoms and peak ALT activity coincided with the height of HDV RNA and HDAg antigenemia. A loss of HDAg and HDV RNA from serum was followed by the appearance of delta antibody in serum only after the patient had been symptomatic for six weeks. Hepatitis B surface antigen was first noted to be absent in August 1983. Assays for HBsAg, HBeAg, HBV DNA, and polymerase have remained negative in the subsequent 41 months of follow-up. The patient was last seen August 1986, at which time he was asymptomatic and the results of a physical examination were normal. There was no detectable interferon in any serum specimen shown on Figure 1 (data not shown).

A liver biopsy was not done during the acute illness, but liver biopsy specimens 5, 10, and 22 months after the onset of delta virus infection did not reveal the presence of delta antigen by immunofluorescence. The biopsy specimens did not show any major changes in architectural distribution, erosion of the limiting plate, or fibrosis from the pretreatment biopsy, although lobular activity had decreased somewhat.

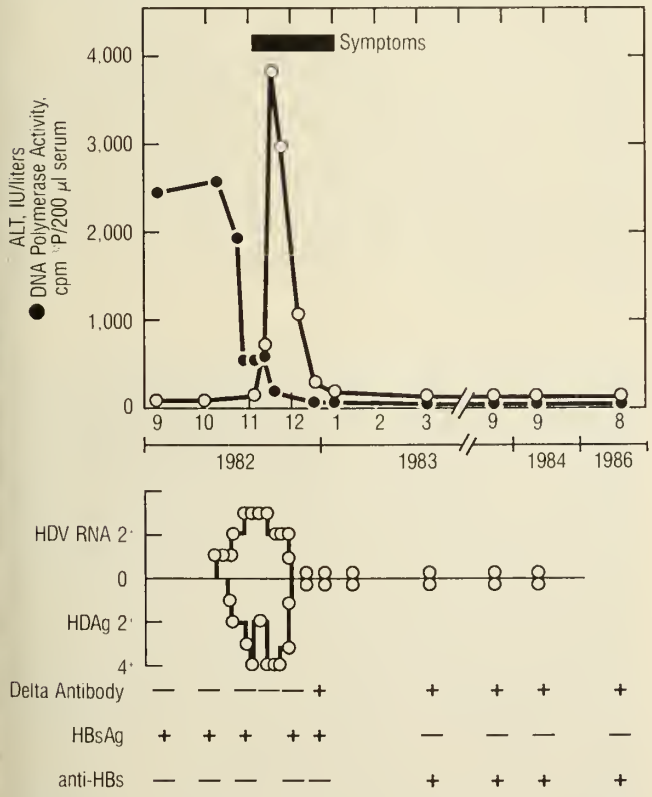

Figure 1.—The graphs show the clinical course (the numbers 9, 10, 11, and so forth signifying the months) and virologic activity of a patient with acute delta hepatitis. ALT=alanine aminotransferase, anti-HBs=antibody to HBsAg, cpm =counts per minute, HBsAg=hepatitis B surface antigen, HDAg=hepatitis D antigen, HDV=hepatitis D virus, + =positive, – =negative

Discussion

Our analysis of the acute delta virus infection occurring in this patient with acute and chronic hepatitis B allows us to examine common features with woodchucks and chimpanzees experimentally infected with delta virus. The appearance of HDAg and HDV RNA in serum is accompanied by a fall in markers of active HBV replication.[2,9] At the height of the viremic phase (by HDAg and HDV RNA), symptoms began and signs of clinical liver disease (elevated ALT level) were seen. The fall in viremia is accompanied by a resolution of symptoms and signs of liver disease and is then followed by the development of anti-delta antibodies, which in our patient have been present for the following 45 months. No estimate of the incubation period is possible in our patient because of his multiple sexual encounters before his acute delta hepatitis. These contacts were the only known possible exposure to HDV and suggest that his sexual activity led to his acute delta hepatitis. In the hepadnavirus-carrier animals, the first signs of delta virus infection occurred 1 to 5 weeks after inoculation in the woodchuck and 4 to 13 weeks after inoculation in the chimpanzees.[2,9]

This patient eventually lost all markers of HBV replication and HBsAg, and anti-HBs antibodies developed that have persisted over a 28-month follow-up. This occurred in spite of his HIV infection and coincident with his adenosine arabinoside monophosphate treatment. A loss of HBsAg after superinfection with HDV is unusual; the usual outcome is a rapid progression to severe forms of chronic hepatitis B.[4,16] Only 1 of 60 other patients without delta hepatitis and 0 of 3 patients with previous delta hepatitis in our ara-AMP trial had this favorable virologic response,[11] and few established HBsAg carriers lose HBsAg over time.[17] It is tempting to speculate that the interference of delta virus infection with HBV replication had a positive effect that enabled the immune system to clear HBV-infected cells. This event was not accompanied by the appearance of serum interferon, a phenomenon that had been reported by Davis and colleagues in an HBsAg carrier with superimposed acute hepatitis A.[18] The fact that our patient had clearing of his HBV infection despite evidence of an HIV infection (the presence of anti-HIV antibodies confirmed by Western blot and otherwise unexplained lymphadenopathy) makes us reexamine the notion that HIV infections in HBV carriers lead to the inability to clear HBV.[19,20]

The cases of three patients with similar permanent HBsAg clearance following a delta virus infection have been previously described.[21] In only one of the three was a seroconversion from anti-delta antibody-negative to -positive observed during the episode of acute icteric hepatitis; the other two were diagnosed by the transient presence of immunoglobulin IgM anti-delta antibody. No HDV RNA or HDAg tests were done on these three subjects. Follow-up periods varied from eight months to four years. We think these three cases may also illustrate the phenomenon seen in our study subject.

Experience with this patient shows that a reliance on anti-delta antibody titers during the acute icteric phase of the illness may miss acute delta virus hepatitis unless these studies are repeated during convalescence or liver tissue is available to allow the detection of delta antigen.[22] The availability of sensitive and specific assays for HDV RNA and HDAg should allow this diagnosis to be made early in the symptomatic phase, as the presence of these markers in

serum precedes the symptomatic illness.[13,14]

In summary, this case illustrates well the clinical-virologic correlates of acute delta virus infection in a human carrier of hepatitis B. We are intrigued by the ability of the delta hepatitis virus to establish an infection and replicate during treatment with a nucleoside analogue, as well as the ability of this patient with a simultaneous HIV infection to clear all markers of active HBV and HDV hepatitis.

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Disseminated *Pneumocystis carinii* in a Patient Receiving Aerosolized Pentamidine Prophylaxis

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Pneumocystis carinii is an organism with an almost exclusive predilection for infecting the lungs of immunocompromised patients. It is the most commonly diagnosed opportunistic infection in patients with the acquired immunodeficiency syndrome (AIDS), occurring in from 60% to 70% of these patients. The mortality rate can be as high as 50%.[1] Preventing *P carinii* pneumonia is important because of the rapid rise in mortality with each successive episode of pneumonia. To that end, the combination of trimethoprim and sulfamethoxazole has been used effectively as an oral prophylactic agent in patients infected with the human immunodeficiency virus (HIV) who also have Kaposi's sarcoma.[2] It is not clear whether intravenous pentamidine is suitable for prophylaxis. When given in an aerosolized form, however, pentamidine has been shown to be effective in the treatment of *P carinii* pneumonia[3,4] and in preliminary studies was shown to be an effective prophylactic agent in preventing pneumonia caused by *P carinii*.[5,6] Recently the Food and Drug Administration approved the use of aerosolized pentamidine isethionate for prophylaxis against *P carinii* pneumonia in patients infected with HIV. While this method of administration achieves high levels of the drug in the lungs, it does not produce substantial levels in the serum and, thus, is likely to produce low levels in extrapulmonary tissues.[7] We report a case of a patient with AIDS in whom an unusual syndrome of hypoalbuminemia developed while he was receiving aerosolized pentamidine prophylaxis and who, on autopsy, was found to have widely disseminated *P carinii* that was thought to contribute substantially to his death.

(Berman SM, Shah B, Wyle FA, et al: Disseminated *Pneumocystis carinii* in a patient receiving aerosolized pentamidine prophylaxis. West J Med 1990 Jul; 153:82-86)

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Report of a Case

The patient, a 45-year-old homosexual man, first tested positive for HIV in October 1986. He was admitted to the Long Beach Veterans Administration Medical Center in March 1987 with *Pneumocystis carinii* pneumonia and was given a 21-day course of intravenous pentamidine. Zidovudine therapy was started in May 1987. In November 1987 he had a second bronchoscopically confirmed episode of *P carinii* pneumonia. Therapy consisted of aerosolized pentamidine isethionate at 600 mg per day (diabetes mellitus had developed after the administration of intravenous pentamidine). Over the next 12 months, he had two more episodes of *P carinii* pneumonia, both of which responded to the use of aerosolized pentamidine. The last episode, in November 1988, occurred despite the institution of prophylactic aerosolized pentamidine at 300 mg per month four months previously. At that time, however, he was noted to have a severe retinitis thought to be consistent with cytomegalovirus infection, and he was started on a regimen of ganciclovir (9-[1,3-dihydroxy-2-propoxymethyl]-guanine).

At the time that therapy with ganciclovir was instituted, the patient was noted to have peripheral edema, and liver

ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
ALT = alanine aminotransferase
AST = aspartate aminotransferase
HIV = human immunodeficiency virus
LDH = lactate dehydrogenase
TMP-SMX = trimethoprim-sulfamethoxazole

function tests showed an alkaline phosphatase level of 370 units per liter, a lactate dehydrogenase level (LDH) of 737 units per liter, aspartate aminotransferase (AST; formerly SGOT) 239 units per liter, alanine aminotransferase (ALT; formerly SGPT) 219 units per liter, and a profound hypoalbuminemia with a serum albumin level of 11 grams per liter. The results of a physical examination and chest x-ray film were consistent with bilateral pleural effusions, mild congestive heart failure, and ascites. A nuclear liver-spleen scan revealed generalized hepatocellular dysfunction and multiple areas of reduced translucence in the spleen thought to be consistent with either abscess, tumor, or cystic disease. An abdominal ultrasonogram was interpreted as showing a diffuse process involving the liver, spleen, and kidneys. A computed tomographic scan showed scattered low-density lesions in the liver, spleen, and kidneys along with calcifications within the kidneys.

His shortness of breath abated after diuresis, and he had no respiratory complaints. On December 12, 1988, his liver function tests showed a progressive deterioration with a serum albumin of 8 grams per liter, alkaline phosphatase 1,130 units per liter, LDH 820 units per liter, AST 235 units per liter, ALT 161 units per liter, and γ-glutamyl transferase 228 units per liter. A prothrombin time was 14.4 seconds, and the partial thromboplastin time was 38.8 seconds. A liver biopsy specimen revealed numerous patchy areas of necrosis with a "foamy" infiltrate on hematoxylin and eosin stain but without an inflammatory infiltrate around these areas of necrosis. No granulomas were seen. A Gomori methenamine-silver stain showed no organisms; in particular, no cysts consistent with *P carinii* could be found. An acid-fast stain was negative, and cultures for bacteria, acid-fast bacilli, and viruses were all negative. Serologic tests for hepatitis A and B were also negative. A 24-hour urine collection showed less than 0.005 grams of protein. His serum albumin value continued to decrease, eventually reaching 2 grams per liter.

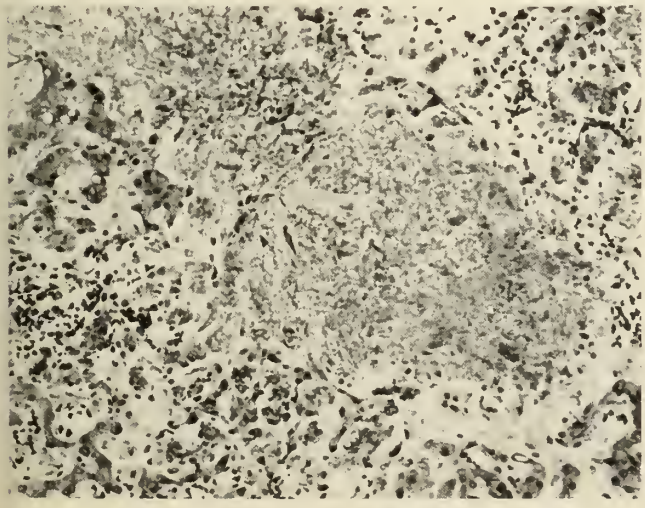

Figure 1.—At autopsy, a specimen of liver shows a miliary "foamy" area (hematoxylin and eosin stain, original magnification × 200).

During the hospital stay he received several transfusions of salt-poor albumin. Each transfusion resulted in a rise in his serum albumin level, but the increase was transient, and his albumin would quickly fall back to 2 grams per liter. The patient's condition deteriorated, and he died on January 15, 1989. After his death, a culture of his peritoneal fluid from December 30, 1988, grew *Mycobacterium avium-intracellulare.*

At autopsy, the lungs displayed firm, pale areas. The lymph nodes were enlarged and dark, and the spleen was enlarged with 2- to 4-mm miliary lesions that were noted also in the liver and both kidneys. In the spleen, lymph nodes, bone marrow, heart, stomach, liver, pancreas, adrenal glands, and kidneys, there were foamy or vacuolated necrotic areas containing fibrin and sometimes visible calcium (Figure 1). These foamy areas resembled those noted in the lungs that were shown to contain *P carinii.* This was confirmed by the finding of a small number of typical *Pneumocystis* organisms in most of the suspect (foamy-appearing) extrapulmonary sites (Figures 2 and 3). In addition, a moderate number of acid-fast bacilli were seen in the

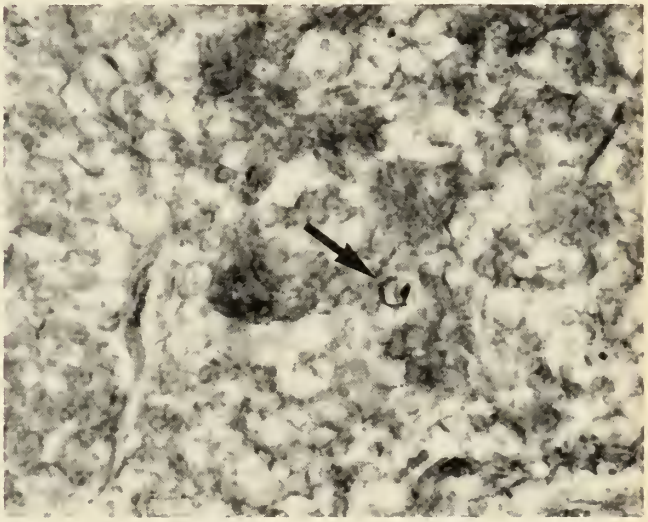

Figure 2.—A specimen of liver shows a "foamy" area with a cyst form of *Pneumocystis carinii* in the center of the area **(arrow)** (Gomori methenamine-silver stain, original magnification × 1,000).

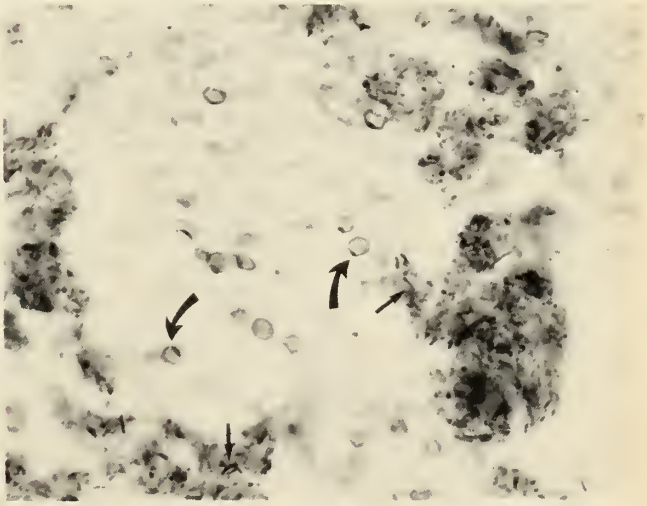

Figure 3.—A specimen of adrenal gland shows a cluster of *Pneumocystis carinii* in the central foamy area **(curved arrows).** Macrophages filled with acid-fast bacilli **(straight arrows)** are seen in the lower portion (Gomori methenamine-silver stain, original magnification × 1,000).

macrophages of the lymph nodes, spleen, liver, and adrenal glands. Cultures of specimens from the liver and spleen grew *M avium-intracellulare*. No evidence of necrosis or inflammation was seen around these organisms or within or near the foamy-appearing areas that contained the *Pneumocystis* organisms.

Discussion

Pneumocystis carinii is a well-known cause of pneumonitis in immunocompromised patients. What is rarely recognized is the fact that *P carinii* can disseminate and infect extrapulmonary sites. Before the discovery of AIDS, there were several widely scattered reports of extrapulmonary pneumocystosis.[8-18] With the advent of AIDS, several more cases of extrapulmonary pneumocystosis have been reported.[19-35] We found 32 reported cases of disseminated *P carinii* in the English-language literature (Table 1). In all 14 of the non-AIDS cases in which *P carinii* was found in extrapulmonary sites the patients had some form of immunocompromise, ranging from hypogammaglobulinemia or agammaglobulinemia to cancer chemotherapy to immunosuppressive therapy after a renal transplant. All of these cases ended in the death of the patient, and in only four was the diagnosis made antemortem. One patient received primaquine phosphate, an antimalarial drug with some activity against *P carinii*. No other patient received therapy that would be considered even partially effective against *P carinii*. In addition, *P carinii* was found in the lungs of all 14 of these patients at autopsy.

One case, patient 3 (Table 1), was strikingly similar to that of our patient. That patient also had *P carinii* in his liver, and he, too, presented with pronounced edema, ascites, and a severe hypoalbuminemia that defied diagnosis until his death.

TABLE 1.—Pneumocystis carinii *Infection With Extrapulmonary Involvement*

Patient	*Sites of Infection With* P carinii	*Immunosuppressive Condition*	*Anti-*P carinii *Therapy*	*Outcome*	*Reference*
1.	Lungs, hilar lymph node	Undetermined	None	Death	Anderson and Barrie, 1960[8]
2.	Lymph nodes (tracheal)	Agammaglobulinemia	None	Death	Livingstone, 1964[9]
3.	Lungs, liver, spleen, lymph nodes, bone marrow	Hypogammaglobulinemia (idiopathic hypoproteinemia)	Primaquine phosphate	Death	Jarnum et al, 1968 [10]
4.	Lung, lymph nodes, spleen	Hypogammaglobulinemia	None	Death	Barnett et al, 1969[11]
5.	Lungs, lymph nodes	Hypogammaglobulinemia	None	Death	Barnett et al, 1969[11]
6.	Lungs, lymph nodes	Leukemia with chemotherapy	None	Death	Barnett et al, 1969[11]
7.	Lungs, lymph nodes, liver, colon, pericardium, pancreas, bone marrow	Renal transplant; steroid therapy	None	Death	Awen and Baltzan, 1971[12]
8.	Lungs, lymph nodes, thymus	Agammaglobulinemia	None	Death	Burke and Good, 1973[13]
9.	Lungs, lymph nodes, spleen	Hypogammaglobulinemia	None	Death	LeGolvan and Heidelberger, 1973[14]
10.	Lungs, heart, liver, stomach, small intestine, spleen, kidneys, bone marrow	Thymic alymphoplasia	None	Death	Rahimi, 1974[15]
11.	Lungs, blood vessel walls, lymph node	Hypogammaglobulinemia	None	Death	Henderson et al, 1974[16]
12	Lungs, spleen	Leukemia	None	Death	Price and Hughes, 1974[17]
13	Lungs, bone marrow	Hodgkin's disease	None	Death	Rossi et al, 1985[18]
14	Lungs, bone marrow	Lymphoma with chemotherapy	None	Death	Rossi et al, 1985[18]
15	Small intestine, lymph node	AIDS	TMP-SMX	Recovered	Carter et al, 1988[19]
16	Lungs, lymph nodes, adrenal glands, bone marrow	AIDS	None	Death	Unger et al, 1988[20]
17	Widely disseminated, including the eyes	AIDS	TMP-SMX	Death	Macher et al, 1987[21]
18	Widely disseminated	AIDS	Intravenous (IV) pentamidine	Death	Grimes et al, 1987[22]
19	Ear (cutaneous)	AIDS	TMP-SMX	Recovered	Coulman et al, 1987[23]
20	Ear	AIDS	TMP-SMX	Recovered	Schinella et al, 1987[24]
21	Lungs, eyes	AIDS	TMP-SMX; IV pentamidine	Death	Kwok et al, 1982[25]
22	Spleen	AIDS	IV pentamidine	Recovered	Pilon et al, 1987[26]
23	Lungs, lymph nodes	AIDS	Aerosolized pentamidine; IV pentamidine	Death	Raviglione et al, 1989[27]
24	Lungs, stomach, duodenum	AIDS	Aerosolized pentamidine	Death	Raviglione et al, 1989[27]
25	Liver, ?eyes	AIDS	Aerosolized pentamidine, TMP-SMX	Recovered	Richie et al, 1989[28]
26	Liver, spleen, kidneys, lymph node	AIDS	Aerosolized pentamidine	Death	Hardy et al, 1989[29]
27	Lymph node, liver	AIDS	Aerosolized pentamidine; trimethoprim and dapsone	Recovered	Sparling et al, 1989[30]
28	Liver	AIDS	Aerosolized pentamidine, IV pentamidine	Recovered	Poblete et al, 1989[31]
29	Spleen	AIDS	Aerosolized pentamidine, IV pentamidine	Recovered	Piot et al, 1989[32]
30	Liver, ?eyes	AIDS	Aerosolized pentamidine, IV pentamidine	Death	Hagopian and Huseby, 1989[33]
31	Widely disseminated, including the lungs	AIDS	Aerosolized pentamidine	Death	Davey et al, 1989[34]
32	Lungs, liver, spleen, lymph nodes	AIDS	None	Death	Afessa et al, 1988[35]

AIDS=acquired immunodeficiency syndrome, TMP-SMX=trimethoprim and sulfamethoxazole

Since 1982 there have been scattered reports of extrapulmonary pneumocystosis in patients with AIDS.[19-35] These cases are different from the previously reported 14 cases. In 14 of 18 cases, the diagnosis of *P carinii* infection was made antemortem. In 11 cases, the patient had at least one episode of pneumonia before the documentation of extrapulmonary *Pneumocystis* organisms. Also, many of the patients with AIDS recovered from their *P carinii* infection.

Of significance are the recent reports of nine cases similar to this one, where the patient was receiving aerosolized pentamidine as prophylaxis against *P carinii* pneumonia.[27-34] These cases are the only ones where the patients had received any prophylaxis against this disease. Preventing *P carinii* pneumonia is important because the mortality increases with each episode. Several studies have shown that it can be effectively prevented in immunosuppressed patients without AIDS.[36-38] In particular, a double-blind study showed trimethoprim-sulfamethoxazole (TMP-SMX) to be highly effective as a prophylactic agent in patients with cancer. Recently, TMP-SMX has been shown to be efficacious in preventing *P carinii* pneumonia in patients with AIDS.[2] The study patients were all HIV-positive, had Kaposi's sarcoma, and had no prior history of opportunistic infections. Over a 24-month period, *P carinii* pneumonia developed in none of 30 patients receiving TMP-SMX, but it did develop in 16 of 30 patients receiving no suppressive therapy. This was a study on primary prophylaxis. Because of this study and much anecdotal evidence, many physicians have advocated prophylaxis against *P carinii* pneumonia for at least all patients who are HIV-positive and who have had at least one episode of the pneumonia.

Many physicians feel that all patients infected with HIV should receive prophylaxis, regardless of whether they have had *P carinii* pneumonia; recent data support this position for patients with CD4 counts of less than 2×10^6 cells per liter (< 200 per μl).[39] Although TMP-SMX was efficacious in the one group of patients studied, its use has not been proved effective yet in other groups of patients with AIDS, specifically in patients who have already had pneumonia. In addition, TMP-SMX is fairly toxic, with a substantial number of patients having bone marrow suppression (especially leukopenia), severe rashes, or both.[40] The marrow toxicity may be magnified in patients who are receiving other marrow suppressive drugs such as zidovudine or ganciclovir. Because of those factors, researchers have been trying to develop prophylactic regimens that are less toxic but effective. Pentamidine isethionate has been shown to be as effective, when given parenterally, as TMP-SMX for the treatment of *P carinii* pneumonia.[41] In addition, pentamidine has also been shown to be effective in the treatment of mild cases of the disease when it is given in an aerosolized form.[3,4] Since that finding, studies were done on the efficacy of aerosolized pentamidine as a prophylactic agent against *P carinii* pneumonia. Preliminary data indicate that it is effective when given once each month.[5] Because of this and the widespread use of similar regimens in the community, the Food and Drug Administration recently approved the use of aerosolized pentamidine as prophylaxis against *P carinii* pneumonia. Given the relative lack of toxicity of aerosolized pentamidine treatments (bronchospasm being the major adverse effect) and the ease of its administration, this form of prophylaxis will likely become the standard of care in the community at large, especially if its effectiveness as prophylaxis against *P carinii* pneumonia is reconfirmed in further trials.

Regardless of when it is acquired or how it is spread, it should be emphasized that *P carinii* causes clinically apparent and significant disease almost exclusively in the lungs; extrapulmonary organs rarely show clinical involvement. This predilection may be exaggerated in HIV-positive patients by our therapeutic interventions, as these patients are often treated empirically for *P carinii* pneumonia with the parenteral administration of TMP-SMX or pentamidine when pulmonary symptoms develop. In doing this we are also treating, or at least suppressing, any *P carinii* that may be located in extrapulmonic tissues. Administering aerosolized pentamidine appears to be a relatively nontoxic method of providing prophylaxis against *P carinii* pneumonia in HIV-positive patients. Because of its pharmacokinetics, however, it does not appear to achieve significant levels in tissues outside of the lungs and thus provides no prophylaxis against extrapulmonary *P carinii*.[7] Trimethoprim-sulfamethoxazole prophylaxis potentially provides both local and systemic protection against *P carinii*, but it is a more toxic agent than aerosolized pentamidine.

Our patient had an extremely unusual presentation, with a profound hypoalbuminemia. On autopsy, organisms consistent with both *P carinii* and *M avium-intracellulare* were found in all tissues examined, including the liver. It is probable that *P carinii* was responsible for the patient's presentation owing to the following:

- The areas of necrosis and obvious pathology in the liver seemed to correspond with the areas in which *P carinii* was found and not with the areas in which the *M avium-intracellulare* was seen.
- Infection with *M avium-intracellulare* is commonly found and reported in HIV-positive patients. An extensive literature review has not elicited any reported cases of *M avium-intracellulare* infection that resemble this case.
- Disseminated *P carinii* infection is a rare event, and there are three cases reported previously that are almost identical in appearance to this case.[10,31,33]

Clinicians should be aware of the possibility of disseminated *P carinii* in patients who receive aerosolized pentamidine for prophylaxis. This therapy appears to be effective in suppressing the formation of pneumonia due to this pathogen. With effective pulmonary prophylaxis helping to prolong life, however, we may be allowing those organisms outside of the lungs time to flourish and thus to cause clinical disease that was previously not seen. In such patients who present with unusual symptoms, particularly those with liver function abnormalities and a decreased serum albumin level, disseminated *P carinii* should be considered in the differential diagnosis. This may be an indication for aggressive workup to look for disseminated *P carinii* or might warrant a switch to empiric parenteral therapy that is also effective against *P carinii*.

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Correspondence

Physical Diagnosis and the Nonexpert Physician

To the Editor: Dr Fitzgerald's review of the literature contrasting the role of physical diagnosis with modern technology in the April 1990 issue[1] is an important contribution to all physicians. What was particularly valuable was how physical findings were placed in a clinical framework of patient or disease outcome. This pragmatic approach to the place of physical diagnosis in the repertoire of physicians is quite useful.

A concern arises when "expert" clinicians are used as the "gold standard." In the review, ophthalmoscopy done by a skilled examiner was more accurate than tonometry in detecting glaucoma. A qualified pediatric cardiologist's assessment of heart disease was not improved by echocardiography, electrocardiography, or chest roentgenography. Finally, the accuracy of the clinical cardiologist's prediction of left ventricular ejection fraction using physical findings was excellent. Most general internists strive to attain physical diagnosis skills at a level comparable to these "expert" clinicians. The lack of acceptance of the general internist's or, for that fact, any nonexpert's examination, as the standard of measurement is disconcerting. The most useful comparison of technology versus physical diagnosis would show how the typical physician—expert and nonexpert—compares with a given test or procedure.

The paradox of the expert is at its height with the physical examination. I have already used this review to demonstrate to medical students and house officers the clinical value of different aspects of physical diagnosis. Can I be sure that the data can be extrapolated to this group who needs it most? Most physicians are not considered "experts" on every part of the physical examination; what is the role of technology in replacing that lack of expertise?

Dr Fitzgerald's review should be a stimulus for all physicians to continually improve physical diagnosis skills. It also can provide a framework for future investigation into the usefulness of the many tools available to clinicians, one of which is the physical examination. I hope future studies will recognize the nonexpert and relatively inexperienced physician as the population who would benefit the most from the results.

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Allergy Screening Tests

To the Editor: The article by Imam and colleagues, reporting on a simple allergy screening test in the March issue,[1] raises several important questions that may challenge the validity of the conclusions drawn.

What is the basis for the implied assertion that a positive intradermal test following a negative skin prick test is a measure of specific immunoglobulin E (IgE), the stated basis for atopy? At least two reports attempting to correlate single-dose intradermal allergy tests and provocation challenges suggest that such positive results are clinically irrelevant.[2,3]

No figures are given on the number of patients judged to be atopic on clinical grounds and subjected to skin testing who were negative. Wouldn't the selection of skin test-positive individuals for in vitro testing skew the results in favor of skin testing being more sensitive? One must assume that not all patients given skin tests in an allergist's office are positive. Might not some of these patients have shown positive results by in vitro testing?

Because 34% of the individual skin test-negative results were positive by the screening test, doesn't this suggest a high level of false-positivity in the screening test? And would this not carry over to affect all the screening test positive results? This may explain the difference between the screening test and the radioallergosorbent test.

Since most allergists conduct skin testing over two or more office visits and all in vitro tests are done overnight after a single blood specimen is drawn, is skin testing really more timely?

A recent study commissioned by the Health Industry Manufacturers Association shows that in vitro tests in the hands of nonallergists are less expensive than skin testing by allergists. The cost of in vitro specific IgE tests has dropped considerably over the past few years. The reference given for the statement that skin tests are more economical is dated 1981.

Skin testing is at best an indirect measure of specific IgE. It is affected by many factors that are difficult to control in an outpatient setting, such as medications previously taken by the patient, diurnal variation in test results, dermatographism, and crosstalk among skin tests. None of these affect the results of in vitro serologic determinations of specific IgE antibody, a direct measure of IgE. A study from Denmark reported at the Berlin meetings of the European Academy of Allergy and Clinical Immunology compares skin testings, in vitro testing (MAST), and bronchial provocation testing (BPT).[4] Correlations of MAST results and BPT were 93%, while skin tests' correlation was 77%. This hardly supports the "benchmark" designation for allergy skin testing.

The concluding statement in the data analysis section on the ideal referral of all screening test-positive patients to an allergist would seem to be so self-serving as to question the objectivity of the investigators.

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* * *

Dr Novey Responds

To the Editor: In questioning the validity of the intradermal diagnostic test, Dr Marinkovich confuses detection of IgE antibodies with clinical relevance. No test for IgE antibodies directly measures clinical disease. The intradermal method, however, is more sensitive and reproducible but less specific than either the scratch or prick techniques, and

it is generally recommended when the prick test is negative or borderline reactive.[1] Moreover, intradermal tests do correlate significantly with bronchial and nasal allergen challenges.[2,3]

The subjects selected for our study were judged atopic on the basis of historical and physical findings of atopic disease; a history relevant to one or more of the allergens tested; and a positive prick or intradermal reaction to one or more of the panel of allergens. The skin tests were used as the benchmark for comparison with the new dipstick test for serum IgE antibodies and to a commercial radioallergosorbent test, which also measures serum IgE antibodies. Negative control subjects had been studied in a previous investigation and were not part of this study.

Most of Dr Marinkovich's remaining remarks focus on the indications for in vivo versus in vitro allergy testing, a topic of vigorous current debate. There are merits and shortcomings of each method. Unfortunately, because of the perceived commercial market for such tests, scientific discussion has been hampered by threats of litigation and other coercions.

The diagnostic test we studied was designed as a screening test for physicians not trained to treat allergic diseases and who feel the need for such a laboratory test. Some experts in the field deplore the use of screening tests and suggest more reliance be placed on a good history and physical examination.

The referral to an allergist may be self-serving, but it at least equally serves the patient. "Allergist" was used in the generic sense of any physician who is qualified to select appropriate allergens for testing, understands the merits and pitfalls of the various tests, can interpret the results and determine the applicability, and can provide an individualized plan of environmental controls and immunotherapy. Such a physician would also acknowledge the danger to a patient of the use of an in vitro test alone to institute antiallergy injections.

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Physician Payment Reform

To THE EDITOR: It is most disconcerting to note that neither the Physician Payment Review Commission nor Dr Lee mentions the necessity of reform of professional liability tort litigation as a vital accompaniment of Medicare—or any other—payment reform.[1]

Perhaps for those who are isolated from clinical medicine, the problem is a quaint abstraction whose surface costs—premiums and defensive medicine—can continue to be passed on to the medical care provider. Ultimately, however, the patient—"consumer" in bureaucratic dialect—will shoulder the brunt of the declining quantity and quality of medical school enrollees, technologic retreats, and pharmaceutical research and marketing cutbacks.

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REFERENCE

1. Lee PR: Physician payment reform—An idea whose time has come (Medical Staff Conference). West J Med 1990; 152:277-284

* * *

Dr Lee Responds

To THE EDITOR: Apparently Dr Levine missed a very important point made in my article with respect to malpractice liability. In order to highlight the issue for the Congress, the Physician Payment Review Commission recommended a separate cost factor for professional liability, and the Congress adopted this recommendation. In addition, the commission has already studied the relationship between practice guidelines and malpractice and this year will be considering broader issues in tort reform. It also should be noted that there are six physician members of the Physician Payment Review Commission. We consider the liability problem to be of major importance and would welcome any suggestions Dr Levine might have regarding the issue.

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Radiologic Case

A Young Man With Recurrent Pulmonary Infections

CARLOS A. CAMARGO, Jr, MPH; GEORGE B. MYCHALISKA, MS; *and* GORDON GAMSU, MD, *San Francisco*

A "Radiologic Case" is published in this format on a regular basis. Physicians interested in contributing to the series are encouraged to send their radiologic cases to the series' editor.

JONATHAN M. LEVY, MD
Series' Editor

A 28-year-old man was seen because of fever and malaise for two days. For ten months he had had recurrent left lower lobe infections for which he had been treated with several antibiotic regimens. One month before admission, these antibiotics were stopped because his infections had apparently resolved. He had no other major medical problems and did not smoke. On physical examination there were decreased fremitus and inspiratory crackles at the lower left hemithorax. The admission chest radiograph (Figure 1) was supplemented by a computed tomographic scan of his chest (Figure 2).

What are the findings?

What is the most likely diagnosis?

How would you confirm this diagnosis?

SEE FOLLOWING PAGE FOR DIAGNOSIS AND DISCUSSION

Figure 1.—A posteroanterior chest radiograph shows two cavitary lesions **(arrows)**, one with an air-fluid level, in the lower left hemithorax. The left lower lobe is more radiolucent than the right.

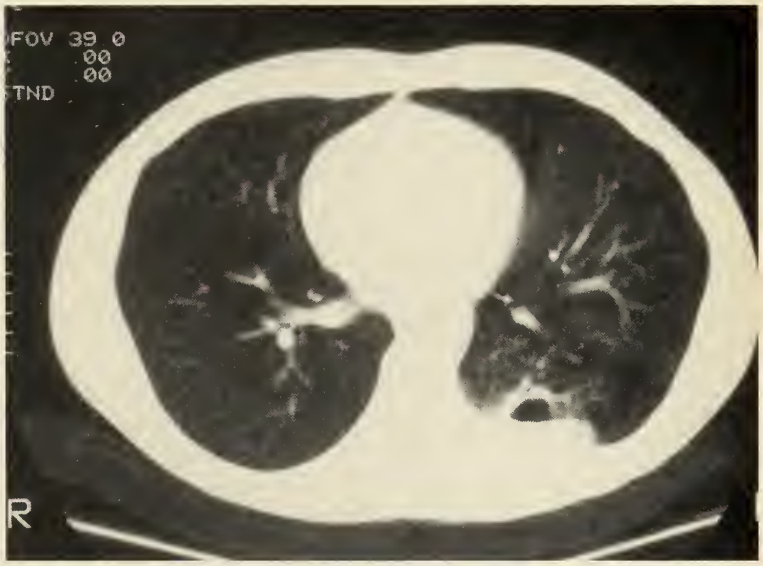

Figure 2.—A computed tomographic scan of the chest shows a cavitary lesion with an air-fluid level in the posterior aspect of the left lower lobe. Multiple cysts are seen in the surrounding lung. The second cavity was imaged lower in the thorax.

(Camargo CA Jr, Mychaliska GB, Gamsu G: A young man with recurrent pulmonary infections. West J Med 1990 Jul; 153:89-90)

Mr Camargo is a fourth-year medical student, and Mr Mychaliska is a third-year medical student at the University of California, San Francisco (UCSF), School of Medicine. From the Department of Radiology (Dr Gamsu), UCSF.

Reprint requests to Gordon Gamsu, MD, Department of Radiology, M-396, University of California, San Francisco, CA 94143.

DIAGNOSIS: Infected intralobar bronchopulmonary sequestration

THE RADIOLOGIC STUDIES showed two cavitary lesions, one with an air-fluid level, in the posterior aspect of the left lower lobe, as well as hyperlucency of the surrounding lung. Although the patient carried a diagnosis of "bacterial lung abscess" and showed improvement on antibiotic therapy, the multicystic changes seemed unusual for this diagnosis. Furthermore, most cystic diseases of the lungs—such as congenital cystic adenomatoid malformation, cystic fibrosis, bronchiectasis, cavitated carcinoma—were considered unlikely given the patient's age, otherwise excellent state of health, and the well-localized nature of his infections. Congenital bronchogenic cysts remained a plausible diagnosis, although these lesions are infrequently subpleural or multiple and should not be surrounded by a hyperlucent lobe. The history and radiologic findings were most suggestive of a developmental disorder called bronchopulmonary sequestration (BPS).

Bronchopulmonary sequestration denotes an area of nonfunctioning lung tissue that lacks a normal connection with the tracheobronchial tree and that is supplied by an aberrant systemic artery usually arising from the descending aorta. Although this disorder probably represents part of a spectrum of "congenital bronchopulmonary-foregut malformations," it has proved useful clinically to consider it as a distinct diagnostic entity. Its prevalence in the general population is not known, but surgical case series have found that a focus of sequestration is encountered in 1% to 2% of all pulmonary resections. When the sequestered lung has not been aerated, bronchopulmonary sequestration presents radiographically as a well-circumscribed, homogeneous opacification. After a connection to the bronchial tree is established, usually subsequent to an infection, the sequestered lung can develop one or more air-containing cysts, with or without air-fluid levels. Air may also enter the sequestration from the surrounding lung through alveolar pores. When the connection is through small parenchymal or bronchial leaks caused by infection, chronic infection of the sequestration invariably follows because of its inadequate bronchial drainage.

Sequestrations may be classified as intralobar or extralobar depending on their pleural investment. In intralobar BPS, which accounts for about 80% of reported cases, the sequestered lung lies within the normal visceral pleura and usually drains into the pulmonary veins. The sequestration is most often located in the posterobasal aspect of the lower lobe (with a slight left-sided predominance) and is infrequently associated with other congenital anomalies. Most cases are discovered as a result of recurrent localized pulmonary infections. The male:female ratio is equal, and approximately 60% of cases present after the age of 10 years.

In extralobar BPS, the sequestered lung is wrapped in its own visceral pleura and usually drains into systemic vessels such as the azygos or hemiazygos veins. The sequestration is most often located posteriorly between the left lower lobe and diaphragm and in more than 50% of cases is associated with other congenital anomalies, especially diaphragmatic hernia. Because the extralobar segment is isolated in its own pleural sac—and therefore less likely to get infected—the typical case is discovered incidentally on a chest radiograph or during repair of an associated congenital defect. The male:female ratio is 4:1, and approximately 60% of cases present before the age of 1 year.

Figure 3.—A digital subtraction aortogram shows a large anomalous vessel **(arrow)** arising from the left side of the descending aorta to supply the left lower lobe. A selective angiogram (not shown) revealed venous drainage into the left inferior pulmonary vein and left atrium.

On the basis of his history and radiologic findings, the patient was tentatively diagnosed as having an infected intralobar bronchopulmonary sequestration. The definitive treatment of infected BPS is surgical excision, and an accurate preoperative diagnosis was considered essential. Aortography is diagnostic by showing the aberrant arterial supply and may also decrease the hazard of intraoperative hemorrhage through unintentional transection of these abnormal vessels. For patients with contraindications to angiography, recent reports suggest that ultrasound and magnetic resonance imaging may be effective, noninvasive methods for defining the vascular anatomy. In this patient, aortography revealed an aberrant arterial blood supply to the left lower lobe with drainage into the pulmonary vein (Figure 3) and thereby confirmed the diagnosis. After a brief course of antibiotics, the patient underwent a curative left lower lobectomy without complications.

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Lessons From the Practice

Due Process

MARK PACKER, *Davis, California*

A young man with close-cropped hair and darting eyes was escorted to the psychiatric ward by police. A third-year medical student, I was the first person to interview him. He told me that he was in the hospital because someone had lied. Someone had told the police he was violent, but he had only been sitting on the porch and whittling. He had gone out to buy a beer for his sister, and when he returned the police took him away.

On the phone his sisters told a different story. The patient had been a "happy-go-lucky, girl-loving guy" until five years ago, they said, when he had lost consciousness after a motorcycle accident. He subsequently became withdrawn and suspicious, harassing neighbors and family members. After ten calls from the family within four months, the police had agreed to bring him to the medical center.

The patient's behavior on the ward confirmed the description his sisters gave us. His paranoia overwhelmed all attempts at communication. When I explained treatment options to him, he said, "You want to experiment on me and I don't like it." He stared at me grimly, then his face melted into a supercilious smirk as if he had just exposed my secret with his stunning repartee.

When I explained the side effects of antipsychotic medications to him, he said, "Oh, I get it, it makes you all jumpy and twitchy." I had not used those particular words, but I thought he might have heard them during a previous hospital stay.

"Did you hear those words somewhere else?" I asked. "They weren't my words."

"Yes, they were your words," he said.

I told him he seemed to like to disagree.

"I'm not disagreeing with you," he said. "I'm just saying my point, which is this." There was a long pause as he put his fingertips together and placed his hands in front of his face. Then he looked sideways at me and fabricated another absurd smile.

I asked if he would like to try the medicine.

"Why should I take something to destroy my brain? I want to remain pure and drug-free. There's nothing wrong with me. I'm sitting here discussing with you in a conversational tone, relaxed." He made an effort to relax his tensed muscles. "I have no dysfunctional order, perhaps. My behavior is adequate. My behavior is perfect."

In fact, his behavior was rather intimidating. During one interview, he extended his hand directly in front of my resident's face, his palm not half an inch from her eyes. He slowly moved his hand across her face, as if trying to erase it from reality. Then he pointed at her chin. "What's wrong with your chin, anyway?" he asked. On another occasion, he took a swing at a patient. "He was shooting shots at me. I got tired of it," he explained. "The nurses told me it was okay to swing at him, just don't do it again. We were just playing a game." In fact, a nurse had told him he would be put in seclusion were anything similar to happen again.

Here, then, was a patient with a disease that made him the object of fear and loathing, a patient who denied the existence of his disease and who refused medical treatment for his disease. If the patient were competent to give informed consent, then his refusal of treatment would have to guide the physician's actions. Legally and ethically, a patient's refusal stands as an absolute contraindication to treatment as long as the patient understands the risks and benefits of possible treatments versus no treatment. If the physician thinks the patient is not competent, and the treatment under consideration is antipsychotic medication, then in California, the patient's lack of competence can only be established in court. Therefore, believing this patient incapable of a rational decision and further believing he would benefit from antipsychotic medication, we filed our petition with the Superior Court.

Several days and many threatening encounters later, two lawyers, one judge, one clerk, one stenographer, one bailiff, and two risk managers filed into our psychiatric unit's conference room. I testified under oath, trying to avoid the patient's piercing glare. I described his understanding of the risks, benefits, and alternatives to medication as he had expressed them to me. Then the attending physician testified as to his diagnostic impression—paranoid schizophrenia. Finally, the patient testified. He said he understood the benefits of the medication as "helping to make my thoughts better." When asked about the risks, he said, "I can quote him," and indicated me. "They make you jumpy and twitchy." Then the judge asked if he thought anything was wrong with him. "Not me. I'm fine. I am drug-free. Like it says in the Bible, purify the temple."

The judge considered a moment, then declared the patient incompetent to make a rational, informed decision. The patient, he said, did not come to a decision by analyzing risks and benefits, nor did the patient give any credence to his physician's opinion. Rather, the patient obstinately clung to the belief that he was completely healthy. He would not listen to reason.

Having achieved the legal aim of getting permission to treat the patient, the attending physician, resident, and I went to see the patient to discuss with him the practical side of administering the medicine. He continued to refuse to take it willingly and began to rave at me. Staring at me, he cried, "You're the lunatic! You're the lunatic! You want to experiment with me, well, fine. You want to cut me open! You want to destroy my brain!" He attacked me then from another angle. "Are you a psychiatrist? No, you're a medical student!" He said it with sneering disdain. I tried to explain that the three of us worked as a team. "I don't want to be on no team," he said. He blustered on, saying we would have to

(Packer M: Due process. West J Med 1990 Jul; 153:91-92)

Mr Packer is a fourth-year medical student at the University of California, Davis, School of Medicine.
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strap him down to inject him. But, finally, under the kind but firm eye of the attending psychiatrist, he leaped to his feet with an angry shout, "All right, I'll take the pills!"

Walking out to my car through the sultry summer evening, it occurred to me what a fantastic expense had gone into preserving this man's rights. The medical center attorney had come from her offices 70 miles away, the entire court staff had been brought to the psychiatric ward, numerous forms had been filled out and filed, and hours had been spent on the phone. I wondered what kind of a nation would go to such expense to respect the rights of one of its most vulnerable citizens, to insure that a truly powerless man was given due process of law. Then I looked up, and waving against the steel blue sky was a flag I suddenly felt terribly proud to call my own.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
STEPHEN J. McPHEE, MD
Series' Editors

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Carcinogenesis, Mutagenesis, Impairment of Fertility—A two-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose-related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a two-year study in mice, there was no evidence of a carcinogenic effect in male mice, although hyperplastic nodules of the liver were increased in the high-dose males as compared with placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups. The rate of hepatic carcinoma in the high-dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement as compared with concurrent controls and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery are not considered evidence of a carcinogenic potential for Axid.

Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, mouse lymphoma assay, chromosome aberration tests, and a micronucleus test.

In a two-generation, perinatal and postnatal fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

Pregnancy—Teratogenic Effects—Pregnancy Category C—Oral reproduction studies in rats at doses up to 300 times the human dose and in Dutch Belted rabbits at doses up to 55 times the human dose revealed no evidence of impaired fertility or teratogenic effect; but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights. On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in one fetus, and at 50 mg/kg, it produced ventricular anomaly, distended abdomen, spina bifida, hydrocephaly, and enlarged heart in one fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers—Studies in lactating women have shown that 0.1% of an oral dose is secreted in human milk in proportion to plasma concentrations. Because of growth depression in pups reared by treated lactating rats, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

Pediatric Use—Safety and effectiveness in children have not been established.

Use in Elderly Patients—Healing rates in elderly patients were similar to those in younger age groups as were the rates of adverse events and laboratory test abnormalities. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

Adverse Reactions: Clinical trials of varying durations included almost 5,000 patients. Among the more common adverse events in domestic placebo-controlled trials of over 1,900 nizatidine patients and over 1,300 on placebo, sweating (1% vs 0.2%), urticaria (0.5% vs <0.01%), and somnolence (2.4% vs 1.3%) were significantly more common with nizatidine. It was not possible to determine whether a variety of less common events was due to the drug.

Hepatic—Hepatocellular injury (elevated liver enzyme tests or alkaline phosphatase) possibly or probably related to nizatidine occurred in some patients. In some cases, there was marked elevation (>500 IU/L) in SGOT or SGPT and, in a single instance, SGPT was >2,000 IU/L. The incidence of elevated liver enzymes overall and elevations of up to three times the upper limit of normal, however, did not significantly differ from that in placebo patients. Hepatitis and jaundice have been reported. All abnormalities were reversible after discontinuation of Axid.

Cardiovascular—In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in two individuals administered Axid and in three untreated subjects.

CNS—Rare cases of reversible mental confusion have been reported.

Endocrine—Clinical pharmacology studies and controlled clinical trials showed no evidence of antiandrogenic activity due to nizatidine. Impotence and decreased libido were reported with equal frequency by patients on nizatidine and those on placebo. Gynecomastia has been reported rarely.

Hematologic—Fatal thrombocytopenia was reported in a patient treated with nizatidine and another H_2-receptor antagonist. This patient had previously experienced thrombocytopenia while taking other drugs. Rare cases of thrombocytopenic purpura have been reported.

Integumental—Sweating and urticaria were reported significantly more frequently in nizatidine- than in placebo-treated patients. Rash and exfoliative dermatitis were also reported.

Hypersensitivity—As with other H_2-receptor antagonists, rare cases of anaphylaxis following nizatidine administration have been reported. Because cross-sensitivity among this class has been observed, H_2-receptor antagonists should not be administered to those with a history of hypersensitivity to these agents. Rare episodes of hypersensitivity reactions (eg, bronchospasm, laryngeal edema, rash, and eosinophilia) have been reported.

Other—Hyperuricemia unassociated with gout or nephrolithiasis was reported. Eosinophilia, fever, and nausea related to nizatidine have been reported.

Overdosage. Overdoses of Axid have been reported rarely. If overdosage occurs, activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. Renal dialysis for four to six hours increased plasma clearance by approximately 84%.

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(Continued from Page 14)

October 20—**30th Annual Scientific Symposium on Kidney Disease.** National Kidney Foundation of Southern California at Wyndham Palm Springs. Sat. Contact: Sylvie Tarro, 5777 W Century Blvd, Ste 395, Los Angeles 90045. (213) 641-8152.

November 2-3—**Update on Thyroid Disease—1990.** UCSF at Hyatt Regency Embarcadero, San Francisco. Fri-Sat. 12 hrs. $150. Contact: UCSF.

PEDIATRICS

September 7-8—**Pediatrics and Environmental Health: The Pediatrician as Investigator, Educator, and Advocate.** Children's Hospital Oakland at Berkeley Conference Center. Fri-Sat. 12 hrs. $85. Contact: Joy Carlson, EPI Training Project, 5900 Hollis St, No. E, Emeryville 94608. (415) 540-3657.

October 7-14—**15th Annual Pediatrics for the Practitioner.** Memorial/UCI Center for Health Education at Mauna Kea Hotel, Hawaii. 1 week. Contact: UCI.

November 9-11—**Infectious Diseases in Children.** Children's Hospital Oakland at Monterey Plaza Hotel on Cannery Row. Fri-Sun. 12 hrs. $280. Contact: Kim Leadon, 747 52nd St, Oakland 94609. (415) 428-3021.

PSYCHIATRY

August 2-4—**Sexual Problems of Adults Molested as Children.** UCLA at Disneyland Hotel, Anaheim. Thurs-Sat. 13 hrs. $375. Contact: UCLA.

October 19-21—**Creating an Integrated Psychiatry: Challenge of the 90's.** California Psychiatric Association at Claremont Hotel, Berkeley. Fri-Sun. 11 hrs. Contact: Barbara Gard, 1100 N St, Ste 2-E, Sacramento 95814. (916) 442-5196.

November 9-11—**36th Annual Group Therapy Symposium.** UCSF at Sir Francis Drake Hotel, San Francisco. Fri-Sun. Contact: UCSF.

November 12-16—**Introduction to Medical Hypnosis.** UCSD at Inn at Del Mar. Mon-Fri. Contact: UCSD.

RADIOLOGY

July 22-26—**Napa Valley Imaging Update: MRI 1990.** UCD at Silverado Country Club, Napa. Sun-Thurs. 17 hrs. $445. Contact: UCD.

July 23-25—**Musculoskeletal Imaging.** Hoag Memorial Hospital, Department of Radiology at Ritz-Carlton Resort Hotel, Laguna Niguel. Mon-Wed. 15 hrs. $350. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 26-29—**4th Annual Symposium on Magnetic Resonance Imaging.** Hoag Memorial Hospital, Department of Radiology at Ritz-Carlton Resort Hotel, Laguna Niguel. Thurs-Sun. 22 hrs. $425. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

August 17-19—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton Resort Hotel, Laguna Niguel. Fri-Sun. 18 hrs. $400. Contact: UCSD.

August 18-19—**Intravascular Ultrasound Imaging.** Memorial/UCI Center for Health Education at Anaheim Hilton Hotel. Sat-Sun. Contact: UCI.

August 23-28—**6th Annual Physics and Biology of Radiology.** UCSD at Hanalei Hotel, San Diego. Thurs-Tues. 25 hrs. $395. Contact: UCSD.

September 6-8—**6th Annual Sonography Update Conference and Exhibit.** UCSD at Hotel del Coronado, San Diego. Thurs-Sat. 18 hrs. $395. Contact: UCSD.

September 7-10—**6th Annual Sonography Update for Physicians and Sonographers.** UCSD at Hotel del Coronado, San Diego. Fri-Mon. 18 hrs. $375. Contact: UCSD.

September 8-9—**Sonography Registry Review.** UCSD at Hotel del Coronado, San Diego. Sat-Sun. 16 hrs. $200. Contact: UCSD.

October 6-7—**Ultrasound: 1990.** UCD at Red Lion Inn, Sacramento. Sat-Sun. 10 hrs. $195. Contact: UCD.

October 20-21—**Advanced Imaging of the Musculoskeletal System.** UCSD at Hotel del Coronado. Sat-Sun. 12 hrs. $125. Contact: UCSD.

October 22-26—**15th Annual San Diego Postgraduate Course.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 27 hrs. $300. Contact: UCSD.

October 26-28—**10th Annual Interventional Radiology.** UCSD at Hotel del Coronado, San Diego. Fri-Sun. 18 hrs. $350. Contact: UCSD.

November 9-11—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton Resort Hotel, Laguna Niguel. Fri-Sun. 20 hrs. $400. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

December 7-9—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton Resort Hotel, Laguna Niguel. Fri-Sun. 18 hrs. $400. Contact: UCSD.

SURGERY

September 1990-December 1990—**Temporal Bone Surgical Dissection Courses: 1990.** House Ear Institute, 5 days per month. 53 hrs. $975. Contact: Antonio De la Cruz, MD, Director of Education, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

July 17-21—**6th Annual Superficial Anatomy and Cutaneous Surgery.** UCSD at La Jolla Marriott. Tues-Sat. Contact: UCSD.

August 8-11—**Sharp Surgical Review Course.** Sharp Memorial Hospital at Le Meridien Hotel, San Diego. Wed-Sat. 14 hrs. $350. Contact: Sharp Memorial, 7901 Frost St, San Diego 92123. (619) 541-3525.

October 6-8—**Anatomic Basis for Aesthetic Surgery: Hands-On Laboratory Course.** UCD at Hyatt Regency, Davis. Sat-Mon. Contact: UCD.

OF INTEREST TO ALL PHYSICIANS

July 19-22—**Radiology for Non-Radiologists.** UCSD at Hotel del Coronado, San Diego. Thurs-Sun. 26 hrs. $295. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077. (404) 641-9773.

July 23-27—**4th Annual Sports Medicine.** UCSD at San Diego Princess. Mon-Fri. Contact: UCSD.

September 10-14—**Hyperbaric Medicine.** UCI/Memorial Medical Center at Long Beach. Mon-Fri. 30 hrs. $650. Contact: Celia Loney, 2801 Atlantic Ave, PO Box 1428, Long Beach 90891. (213) 595-2000.

November 9-10—**2nd Annual Symposium—Diagnosis and Treatment of Bone and Soft Tissue Tumors: A Multidisciplinary Approach.** UCD at Hyatt Regency, Sacramento. Fri-Sat. 14 hrs. $345. Contact: UCD.

November 12-16—**Hyperbaric Medicine.** UCI/Memorial Medical Center at Long Beach. Mon-Fri. 30 hrs. $650. Contact: Celia Loney, 2801 Atlantic Ave, PO Box 1428, Long Beach 90801. (213) 595-2000.

December 6—**Common Musculoskeletal Problems—Foot and Ankle.** VA Medical Center Sepulveda. Thurs. 5 hrs. Contact: Arun Mehta, MD, Rehabilitation Medicine Service (117), VAMC Sepulveda 91343. (818) 895-9344.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

July 18-21—**Insulin Dependent Diabetes.** Barbara Davis Center for Childhood Diabetes, the Children's Diabetes Foundation, and CU School of Medicine at Keystone Inn, Keystone. Wed-Sat. Contact: U of Colo.

July 23-27—**3rd Annual Colorado Geriatric Symposium.** U of Colo at the Given Institute, Aspen. Mon-Fri. Contact: U of Colo.

July 30-August 3—**Dynamic Psychotherapy.** U of Colo at the Given Institute, Aspen. Mon-Fri. Contact: U of Colo.

August 5-9—**Annual Pediatric Program.** U of Colo at the Given Institute, Aspen. Sun-Thurs. Contact: U of Colo.

(Continued on Page 96)

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(Continued from Page 94)

August 6-8—**Newborn Respiratory Therapy Traineeship.** The Children's Hospital, Denver. Mon-Wed. Contact: Jeff Griebel, (303) 861-6227.

August 6-10—**Respiratory Therapy Traineeship.** The Children's Hospital, Denver. Mon-Fri. Contact: Jeff Griebel, (303) 861-6227.

August 12-18—**Annual Primary Care Orthopedics.** U of Colo at the Given Institute, Aspen. One week. Contact: U of Colo.

August 14-18—**Aspen Basic/Clinical Science: Neuroscience.** U of Colo at the Given Institute, Aspen. Tues-Sat. Contact: U of Colo.

August 20-24—**Annual Internal Medicine Board Review.** U of Colo, Denver. Mon-Fri. Contact: U of Colo.

September 4, 11, 18—**OB Nursing in the 1990s.** The Children's Hospital at University Hospital, Denver. Tues. Contact: Trish Beachy, (303) 270-8376.

September 10-14—**Family Practice Review.** U of Colo, Denver. Mon-Fri. Contact: U of Colo.

October 10-11—**Physician Preceptorship Program.** The Children's Hospital, Denver. Wed-Thurs. Contact: Pat Winter, (303) 861-6668.

October 17-19—**Care of the Sick Newborn Conference.** The Children's Hospital, Denver. Wed-Fri. Contact: Conference Dept, Children's Hospital, (303) 861-6945.

October 22-26—**Rural Perinatal Traineeship (Level 1).** The Children's Hospital, Denver. Mon-Fri. Contact: Christie Sievers, (303) 861-5413.

November 2-3—**Fort Collins Perinatal Conference.** The Children's Hospital at the Marriott Hotel, Fort Collins. Fri-Sat. Contact: Christie Sievers, (303) 861-6413.

November 9-10—**Western Slope Conference.** The Children's Hospital at the Red Lion Inn, Durango. Fri-Sat. Contact: Christie Sievers, (303) 861-6413.

November 12-16—**Rural Perinatal Traineeship (Level II).** The Children's Hospital, Denver. Mon-Fri. Contact: Christie Sievers, (303) 861-6413.

December 3-7—**Respiratory Therapy Traineeship.** The Children's Hospital, Denver. Mon-Fri. Contact: Jeff Griebel, (303) 861-6227.

January—**Perinatal Continuing Education Program.** The Children's Hospital, Denver Community Hospital-based, 40-week, self-study program for all perinatal healthcare providers. Contact: Pat Winter, (303) 861-6668.

CONTACT INFORMATION

U of Colo—Contact. University of Colorado School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver, CO. (303) 270-5195.

IDAHO

July 26-28—**Idaho Medical Association—Annual Meeting.** Sun Valley. Thurs-Sun. Contact: Idaho Medical Association, 305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

July 19—**Neonatal Resuscitation.** St Vincent Hospital, Santa Fe. Thurs. Contact: Jennifer Johnson, MD, 455 St Michael's Dr, Santa Fe 87501. (505) 983-3361.

July 19-21—**Current Concepts in General Surgery.** Hilton Hotel, Albuquerque. Thurs-Sat. Contact: UNM SOM, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

July 21—**Casting Traction and Orthonics: A Hands-On Experience.** Marriott Hotel, Albuquerque. Sat. Contact: Rebecca Carpenter, RN, St Joseph Medical Center, 400 Walter, NE, Albuquerque 87102. (505) 848-8610.

August 16—**Neonatal Resuscitation.** St Vincent Hospital, Santa Fe. Thurs. Contact: Jennifer Johnson, MD, 455 St Michael's Dr, Santa Fe 87501. (505) 983-3361.

September 6-8—**Perinatal Care Update.** Hilton Hotel, Albuquerque. Thurs-Sat. Contact: UNM SOM, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

September 7—**The Wounded Healer: Becoming a Healthy Healer.** Memorial Hospital, Albuquerque. Fri. Contact: Janice Frank, 806 Central, SE, Albuquerque 87102. (800) 448-9238 or (505) 247-0220.

September 14-15—**Essentials of Health Care for the Elderly.** Albuquerque Convention Center. Fri-Sat. Contact: UNM Office of Continuing Medical Education, PO Box 713, Albuquerque 87131. (505) 277-3942.

September 21-22—**Southwest Psychiatric Symposium on Substance Abuse.** Hyatt Regency, Albuquerque. Fri-Sat. Contact: UNM Office of Continuing Medical Education, PO Box 713, Albuquerque 87131. (505) 277-3942.

October 4-6—**Management of Radiation Accidents.** Sheraton Old Town Hotel, Albuquerque. Thurs-Sat. Contact: UNM Office of Continuing Medical Education, PO Box 713, Albuquerque 87131. (505) 277-3942.

October 11-13—**Second International Symposium on Intrapartum Biochemical Monitoring of the Fetus.** Hyatt Regency, Albuquerque. Thurs-Sat. Contact: UNM Office of Continuing Medical Education, PO Box 713, Albuquerque 87131. (505) 277-3942.

October 12-13—**John N. Wilson, MD: Lectureship in Cardiovacular Diseases.** Hyatt Regency, Albuquerque. Fri-Sat. Contact: Ann Nelson, Presbyterian Heart Institute Foundation, PO Box 26666, Albuquerque 87125. (505) 841-1225.

October 19-20—**Cancer Update 1990.** Clarion Four Seasons Hotel, Albuquerque. Contact: UNM Office of Continuing Medical Education, PO Box 713, Albuquerque 87131. (505) 277-3942.

October 20-21—**Common Problems in Pediatric Pulmonary Disease.** Santa Fe Hilton. Contact: Joe Dean, MD, 813 N Washington, Roswell 88201. (505) 622-2606.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

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MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

July 25-27—**12th Annual Common Problems in Pediatrics** (Sponsor: UUMC). Wed-Fri. University Park Hotel, Salt Lake City. Contact: (801) 466-3500.

October 4-5—**Ethics and Health** (Sponsor: UUMC). Thurs-Sat. University of Utah Alumni House, Salt Lake City. Contact: (801) 581-8664.

October 11-12—**Proper Prescribing of Controlled Substances** (Sponsor: UMA and UUMC). Thurs-Fri. University Park Hotel, Salt Lake City. Contact: UMA.

SPONSORS OF COURSES—ABBREVIATIONS

AHA: American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.

BYUHS: Brigham Young University Health Services, McDonald Student Health Center, Brigham Young University, Provo 84602. (801) 378-2771.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 S 300 East, Salt Lake City 84101. (801) 262-3461.

DMC: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 673-9681.

HCH: Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

144: 144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave, Salt Lake City 84103. (801) 363-1221.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

SMH: St Mark's Hospital, 1200 E 3900 South, Salt Lake City 84117. (801) 268-7111.

UMA: Utah Medical Association, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUMC: University of Utah Medical Center, 50 N Medical Dr, Salt Lake City 84132. (801) 581-2258.

UVRMC: Utah Valley Regional Medical Center, 1034 N Fifth West, Provo 84604. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

VVMC: Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.

(Continued on Page 98)

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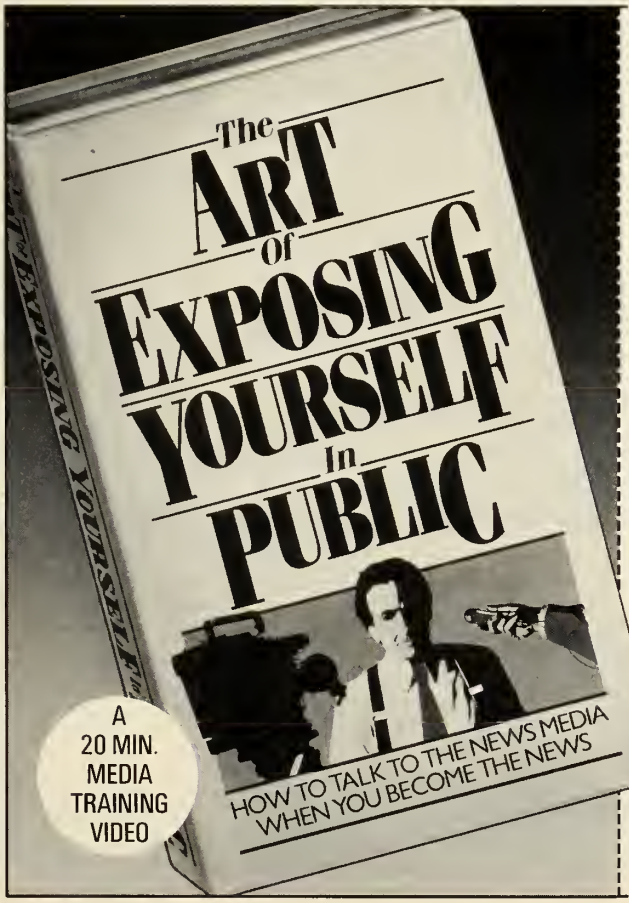

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CONTINUING MEDICAL EDUCATION

(Continued from Page 97)

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

August 2-4—**Imaging.** Coeur d'Alene Resort. Thurs-Sat. Contact: Sacred Heart Medical Center, Dept of Radiology, (509) 455-3352.

August 9-10—**Pacific NW Vascular Symposium.** Seattle. Thurs-Fri. Contact: Swedish Hospital, (206) 386-2265.

September 20—**Orthopedics.** Everett. Thurs. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

September 20-21—**Critical Care 90.** Tacoma. Thurs-Fri. Contact: Multicare, (206) 594-1221.

October 11—**Diabetes.** Everett. Thurs. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

October 16-19—**Indoor Radon and Lung Cancer: Reality or Myth.** Richland. Tues-Fri. Life Sciences Center, Battelle, Pac NW Lab. (509) 376-3665.

October 19—**24th Annual Cancer Conference: Gastrointestinal Cancer in the 90s.** Seattle. Fri. Contact: VMMC.

October 20—**Practice Update for Rural Physicians.** Seattle. Sat. Contact: VMMC.

November 2—**Diabetes, 1990.** Seattle. Fri. Contact: VMMC.

November 8—**Pediatrics.** Everett. Thurs. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

November 9—**Medical and Surgical Update for Psychiatrists.** Seattle. Fri. Contact: VMMC.

December 7—**Practical Pediatrics.** Seattle. Fri. Contact: VMMC.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact. Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104 (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

WYOMING

August 8-11—**American College of Surgeons, Montana-Wyoming Chapter.** Jackson Hole. Wed-Sat. Contact: Robert C. Ratcliff, MD, 940 E Third St, Casper 82601. (307) 577-4223. ◆

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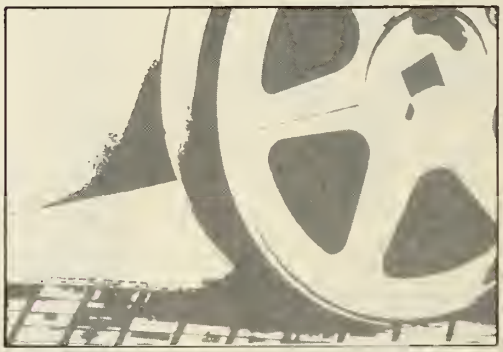

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The abstract (approximately 150 words) should be a short summary, saying in brief what is said at length in the body of the article—rather than such and such "is discussed," "is presented," or "was investigated."

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Tables

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Three sets of clear, unmounted black and white glossy prints of figures should be submitted (preferably 5 by 7 inches, but no larger than 8½ by 11 inches). For line drawings, original artwork or glossy prints are acceptable. Illustrations should be numbered consecutively in Arabic numerals and the position indicated in the text. Figure number, first author's name and top of the photo should be shown on the reverse side of each illustration. Recognizable photographs of patients are to be masked and written permission for publication obtained from the patients.

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References

References should be limited to those cited in the text and should be to medical, scientific, or scholarly publications. (Mass circulation periodicals are referenced in parentheses in the text.) They must be typed double-space and numbered consecutively as they appear in the manuscript. (See examples below for style.) Abbreviations of journal titles should conform to those used in *Index Medicus*.

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Note handling of multiple authorship. If more than three authors are listed as contributors, use "et al" to designate those names after the first three. Also note capitalization, punctuation, use of inclusive page numbers, and year of publication. Separate the subtitle from the title by either a dash or a colon. Use colon *only* if it appears in the original citation.

1. Jones JS, Anderson HW, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978; 292:444-456
2. Graybill JR, Alford RH, Smith RG, et al: Cell-mediated immunity in cryptococcosis: A brief review. Cell Immunol 1978; 7:76-79

Books

Note handling of "edition," "editor(s)," and "volume," as well as appropriate sequence of reference information and capitalization of chapters and titles.

3. Berne EJ, Smith TL: Role playing in therapy, chap 2, Principles of Group Therapy. New York, Oxford University Press, 1966, pp 35-51 *(author of chapter same as author of book)*
4. Munsung JM: The role of drugs, chap 2, *In* Brest AN, Mayer JH (Eds): Hypertension—Vol 2, Therapy, 2nd Ed. Springfield, Ill, Charles C Thomas, 1961, pp 456-479 *(author of chapter different from authors of book)*

Pamphlets, Monographs, or Books With No Given Author

5. AMA Department of Drugs: AMA Drug Evaluation, 3rd Ed. Littleton, Mass, Publishing Sciences Group, 1977 *(corporate author)*
6. Compilation of Standard Definitions, 3rd Ed. Philadelphia, American Society for Testing and Materials, 1976 *(no given author; give name and place of publisher)*

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CALIFORNIA AND WESTERN STATES

Opportunities for BE/BC physicians in metropolitan and rural areas in Critical Care, Emergency Medicine, Endocrinology, ENT, Family, Internal Medicine, Neurology, Neurosurgery, OB/GYN, Oncology, Orthopedics, Pediatrics, Pulmonology, Rheumatology, and Urology. **Bradshaw Associates, 21 Altamount, Orinda, CA 94563; (415) 376-0762, FAX (415) 376-0813.**

OB/GYN, INTERNISTS, Family Practitioners, Pediatricians for Arizona and western opportunities. Quality positions available other regions of country. Inquiries confidential. Mitchell & Associates, PO Box 1804, Scottsdale, AZ 85252; (602) 990-8080.

NEAR STANFORD. Six Internists, all subspecialty trained and members of clinical faculty at Stanford, interested in an associate with subspecialty interest and training. Should be well grounded in Internal Medicine. Send CV to Dr Bigler, El Camino Internal Medical Group, 125 South Dr, Mountain View, CA 94040.

CALIFORNIA—NORTHERN. Area's leading private practice group has immediate and future positions for BC/BE Family Practice and Primary Care Physicians in its Department of Ambulatory Care and General Medicine. Excellent compensation, incentive program, full benefits, early equity position, retirement plan. Experience life-style and professional fulfillment in beautiful northern California. Call Maureen Forrester: (408) 282-7833. Send CV to San Jose Medical Group, Inc, 45 S. 17th St, San Jose, CA 95112.

RADIOLOGIST. Part-time position available immediately in small hospital with general radiography and fluoroscopy, mammography and ultrasound in Weaverville, California. Contact Drs Wheeler, Biggs, or Babbitt, West Coast Radiology, 3798 Janes Rd, Ste 12, Arcata, CA 95521; office number (707) 822-3621, ext 191.

PHYSICIAN OPPORTUNITIES IN ARIZONA. Thomas-Davis Medical Centers, PC, a rapidly expanding multispecialty group practice of 90 plus physicians in Tucson, Green Valley, and Tempe, Arizona, has positions available in these cities in Internal Medicine, Pediatrics, OB/GYN, Orthopedics, Urgent Care, and Family Practice. Excellent fringe benefits and profit sharing program. Fee-for-service, as well as owned HMO. Must be BE/BC. Call or write James J. Vitali, CEO, Thomas-Davis Medical Centers, PC, PO Box 12650, Tucson, AZ 85732; (602) 322-8300.

PHYSICIAN OPPORTUNITIES NATIONWIDE

For all specialities for hospitals, clinics, multispecialty groups, partnership and solos. Contact Jim Grant in complete confidence at the bay area specialists. **Nugent & Grant, Inc, 1400 Coleman, Ste B-22, Santa Clara, CA 95090; or call (800) 727-2478, FAX # (408) 727-7390.** Never a fee to the physician.

OB/GYN. Multispecialty group in northwest Washington desires second Obstetrician. Excellent practice opportunity, full range of benefits, early partnership status, all practice costs paid. For more information contact Shane Spray, 1400 E. Kincaid, Mount Vernon, WA 98273; (206) 428-2524.

CALIFORNIA, SANTA CLARA COUNTY. Positions currently available for experienced physicians to provide primary care services at hospital based Urgent Care Center in San Jose. Minimum guarantee of $100,000 plus annually for 42-hour work week, 48 weeks per year with paid malpractice. No night call. Please contact Nanette Peter, Associated Emergency Physicians, Inc, Medical Group of Northern California, 1625 The Alameda, Ste 201, San Jose, CA 95126; (408) 293-8881.

ALBUQUERQUE, NEW MEXICO. BC/BE Family Practitioners sought to join established, private practice, single specialty group practice. Income guarantee, benefits. Please send CV to Kathryn Rhoades, Presbyterian Healthcare Services, PO Box 26666, Albuquerque, NM 87125-6666, or call 1 (800) 545-4030, ext 6330.

FAMILY PRACTICE OPPORTUNITY. Association available in rural town, one hour from Seattle and one-half hour from Tacoma. Obstetrics optional. Growing community close to mountains and Puget Sound. Owner to retire in four to five years. (206) 829-1444.

PEDIATRICIANS, BC/BE to join busy, well established Pediatric practice in San Francisco suburb. Two Pediatricians looking for two full-/part-time associates to replace two retiring partners. Guaranteed salary leading to early partnership. Flexible hours possible. Large patient base means you can be busy from first day. Excellent hospitals with neonatal and pediatric ICUs. University appointments possible. Beautiful San Francisco bay area convenient to ski areas, beaches, wine country. Gerald Harris, MD, Pediatric Medical Group, 1800 Sullivan Ave, Ste 507, Daly City, CA 94015; (415) 756-5150.

PHYSICIANS NEEDED

The continuing growth of our service area population (now 90,000) has created an immediate need for additional 8C/8E physicians in the following specialities:

- **NEUROLOGY.** Establish private practice with no investment, guaranteed income. Proficiency in EEG, EMG required.
- **GENERAL/THORACIC SURGERY.** Establish private practice in General and Thoracic Surgery (no open heart) with no investment, guaranteed income.
- **ONCOLOGY.** Establish private practice with no investment, guaranteed income. Some General Internal Medicine necessary initially.
- **ORTHOPEDIC SURGERY.** No investment, guaranteed income. Above average earning potential.
- **RADIOLOGY.** Hospital group position. Excellent salary and benefit package. Competency in ultrasound, CAT, Nuclear Medicine, film screen mammography, and general diagnosis required. MRI experience desired. Inpatient and outpatient. (California license is required.)

112-bed full service hospital, very well equipped. Excellent ancillary services. Our service area population is now 90,000; a growing area with new businesses and a stable economy.

Located in central California near Sequoia National Park, Tulare offers an excellent family oriented lifestyle and all expected amenities. Beautiful homes, close to hospital and office, are affordably priced. Good schools, many community activities, and abundant recreation including golf, tennis, skiing, mountain and equestrian activities. Easy access to all California's major metropolitan and resort areas.

Contact:

Tulare District Hospital
Physician Recruiting Office
PO Box 90112
Los Angeles, CA 90009
(800) 468-2687

MD TO ASSIST in busy Orthopedic clinic and Operating Room. Will also take call. Position has been used in the past as a bridge to Orthopedic residency. Attractive salary and excellent benefit package. Washington State licensure required. Available immediately. Send CV or contact Mary Anderson, Personnel Representative, Pacific Medical Center, 1200-12th Ave S., Seattle, WA 98144; (206) 326-4111.

WENATCHEE, WASHINGTON, PACIFIC NORTHWEST. Wenatchee Valley Clinic, a 95-physician multispecialty clinic, is seeking a BC/BE General Internist. Guaranteed first year salary, incentive production bonus available. Attractive fringe benefit package. Located on the Columbia River in the sunny eastern foothills of the Cascades. Abundant recreational activities available. Send résumés to Wenatchee Valley Clinic, PO Box 489, Wenatchee, WA 98807, Attn: Julie Zimmerman.

OB/GYN. BC/BE to join 20 physician (OB, Pediatrics, Internal Medicine) practice in sunny central Washington. Reasonable call schedule with three OB/GYN department. Competitive salary, excellent benefit package including vacation at 30 days per year and professional liability. Contact Ann Garza, Yakima Valley Farm Workers Clinic, PO Box 190, Toppenish, WA 98948; (509) 865-5898.

SAN FRANCISCO NORTH BAY AREA/NAPA VALLEY. Immediate openings (career and part-time) in a multidiscipline Emergency Department for physicians trained in Emergency Medicine, Internal Medicine, Family Practice, or Pediatrics. Full in-house multispecialty coverage. Complete generous benefit package. Contact Robert Mack, MD, Kaiser Hospital, 975 Sereno Dr, Dept WJM, Vallejo, CA 94589; (707) 648-6200. EOE.

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(Continued from Page 100)

PHYSICIANS
REGISTERED
PHYSICAL THERAPISTS
PHYSICIAN ASSISTANT

Currently seeking California/Nevada state licensed BC/BE physicians and other medical professionals to perform Workers' Compensation and Personal Injury treatment and evaluation in our many California and Nevada locations. Spanish speaking a plus. Specialties include Neurology, Orthopedic, Internal Medicine, Psychiatry, Plastic Surgery, Occupational Medicine, Industrial Medicine.

We offer:

- Full-time or part-time
- Flexible hours
- Guaranteed income
- Possible expense for relocation
- Will provide training
- Excellent growth potential

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GENERAL SURGERY
ORTHOPEDICS

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CONTACT: **Colleen Mooney, Recruitment Coordinator**
Rockwood Clinic, PS
E. 400 Fifth Ave
Spokane, WA 99202
(509) 838-2531

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(Continued on Page 102)

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- general surgery
- neurosurgery
- colon/rectal surgery
- cardiac/thoracic surgery
- pediatric surgery
- peripheral/vascular surgery
- plastic surgery

you could be eligible for an $8,000 annual stipend in the Army Reserve's Specialized Training Assistance Program.

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(Continued from Page 101)

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Group Health Cooperative of Puget Sound
521 Wall Street
Seattle, WA 98121

or call (206) 448-6546

Group Health Cooperative of Puget Sound

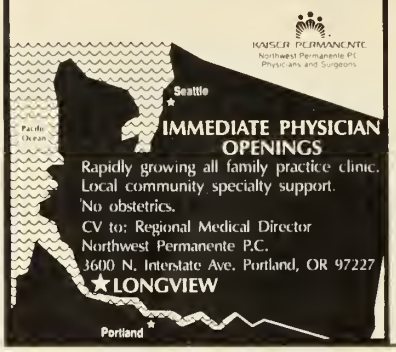
CENTRAL CALIFORNIA. Join our team of Family Practice Physicians in a progressive community health center near Fresno, California. Competitive salary with extra on-call and overtime. Malpractice paid. Generous vacations and time-off policy. Affiliated with UCSF with on-site Family Practice residents and medical students. Varied practice, including Obstetrics, Pediatrics, and in-patient care with an emphasis on health maintenance, patient education, and primary care research. Position is 60 percent clinical, 40 percent teaching. Bilingual English-Spanish helpful. Contact Ardeth Bier, Fresno County Dept of Health, PO Box 11867, Fresno, CA 93775; (209) 445-3353.

URGENT CARE/PRIMARY CARE PHYSICIANS for over 90 positions available with various physician groups in Phoenix metropolitan/Tucson, Arizona. Excellent compensation and partnership opportunities. Contact Mitch Young, PO Box 1804, Scottsdale, AZ 85252; (602) 990-8080.

HAWAII. Family Practitioner needed for rural underserved area. Full-time position in nonprofit community health clinic. No OB, hospitalizations optional. Desire dedicated person to work in multicultural setting. Contact Alan Chun, MD, Waianae Coast Comprehensive Health Center, 86-260 Farrington Hwy, Waianae, HI 96792; (808) 696-7081.

CALIFORNIA MULTISPECIALTY. Cardiologist, Internal Medicine, Pediatrician, Endocrinologist, Orthopedist, General/Family Practitioner, Obstetrician/Gynecologist, Dermatologist, Ophthalmologist, General Surgeon, Podiatrist. Excellent opportunity for physicians in Los Angeles suburb to join 100 member multispecialty medical group. Large fee-for-service and prepaid practice, no Medi-Cal. Excellent compensation program based on guarantee plus incentive, profit sharing and pension plan. Group provides health, dental, life, and malpractice. Partnership in real estate and medical corporation available. Send CV to Ron McDaniel, Assistant Administrator, Mullikin Medical Center–5, 17821 S. Pioneer Blvd, Artesia, CA 90701.

LONGVIEW, WASHINGTON



Longview is a picturesque, stable community of 42,000 located near the Columbia Gorge and the coastal mountains and beaches of Washington and Oregon. Members of our 12-physician group enjoy individual subpractices, infrequent call, and new state-of-the-art medical offices.

We invite you to contact us at the above address regarding practice opportunities. Or call Judy Parmenter, Physician Recruitment, (503) 280-2050 for further information.

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Several positions available for Family Practice, Internal Medicine, and most medical subspecialties. We are a young, aggressive group in a well known prepaid group practice HMO organization with excellent benefits and a very reasonable call schedule. You will have a rewarding practice opportunity with ample time to enjoy the mountains and San Francisco which are nearby. If interested please call or send CV to Physician Recruitment, Administration, The Permanente Medical Group, Inc, 1305 Tommydon St, Stockton, CA 95210; (209) 476-3300.

FAMILY PRACTICE PHYSICIAN. Full-time in a busy walk-in medical clinic. Located in Visalia, California (Tulare County). Malpractice insurance, good salary, etc. Please call (209) 627-5555 for more information.

GENERAL INTERNIST. Multispecialty group located in San Luis Obispo, California, seeks a BC/BE physician. Fringe benefits plus practice costs paid and shareholder status. Submit your CV to Physician Recruitment, San Luis Medical Clinic, 1235 Osos St, San Luis Obispo, CA 93401.

FAMILY PRACTITIONER. Multispecialty group located in San Luis Obispo, California, seeks a BC/BE physician. Fringe benefits plus practice costs paid and shareholder status. Submit your CV to Physician Recruitment, San Luis Medical Clinic, 1235 Osos St, San Luis Obispo, CA 93401.

SAN FRANCISCO BAY AREA multispecialty group seeks Pediatrician BC/BE, to join 26 congenial men and women delivering quality care in a combined fee-for-service, HMO/PPO setting. Bay Valley Medical Group, Attn: Daniel Rowe, MD, 27212 Calaroga Ave, Hayward, CA 94545; (415) 785-5000.

INTERNIST, PEDIATRICIAN to join multispecialty group. Salary with incentive, early partnership. Northern California. Reply to Number 197, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

MULTIPLE FAMILY PRACTICE (BC/BE) positions available in several suburban satellite clinics of a large Seattle area multispecialty group practice. Diverse patient population includes managed care, fee-for-service, and retired military (at some satellite clinics). Competitive salary and excellent benefits. Contact Mary Anderson, Pacific Medical Center, 1200 12th Ave S., Seattle, WA 98144; (206) 326-4111.

ALL SPECIALTIES/DESIRABLE PRACTICE OPPORTUNITIES AVAILABLE

Let us find you the practice that meets your specifications and geographical preference. There is no fee to the physician for our professional service. All inquiries are held in strict confidence. BC/BE physicians send CV or call:

Sharon Mac Kenzie
Mac Kenzie & Associates
PO Box 1240
Trinidad, CA 95570
1 (800) 735-4431

INTERNAL MEDICINE. Long established multispecialty group in central Washington needs Internist. Independent contract or join partnership later. University town with many cultural and recreational activities. Send CV to Medical Building Associates, 200 E. 6th, Ellensburg, WA 98926, or call (509) 925-9891.

GYNECOLOGIST needed for 78-bed JCAHO hospital. We are growing and we need to enlarge our specialty staff. Just opened new Cancer Treatment Center. 12,000 community, 90,000 immediate service area, 160,000 catchment area. Great outdoors area, cattle, oil, gas, hunting, fishing, good schools, low crime, ideal area for raising children. Reasonable malpractice rates. Send CV to Marilyn Bryan, Community Hospital, PO Box 2339, Elk City, OK 73648: (405) 225-2511.

RADIOLOGIST FOR SOUTHEASTERN UTAH. Excellent practice opportunity to join second Radiologist. Primary service area of 30,000 people with 88-bed community hospital. Nuclear, CT, mammography, ultrasound, and radiography. Contact Milton Bauermeister, MD, Castleview Hospital, Price, UT 84501; (801) 637-4800, ext 280 or (801) 472-5403.

FAMILY PRACTITIONER, INTERNIST, PEDIATRICIAN BC/BE for thriving community clinic in ideal southern California climate. Modern facility, planned expansion. Call is optional, flexible scheduling. Diverse population includes working poor, managed care, 50 percent Hispanic; presents opportunities for interesting community medicine. Malpractice covered, competitive salary. Escondido Community Clinic, Tracy Ream, Executive Director, 401 N. Spruce St, Escondido, CA 92025; (619) 747-1867.

MD, BC/BE in Occupational Medicine, Internal Medicine, Family Practice, or ER to join established free-standing Occupational Medicine clinic. Attractive opportunity for growth. Competitive salary and benefits. Send CV to Manager, MBI Industrial Medicine, Inc, 2539 N 35th Ave, Phoenix, AZ 85009.

ORTHOPEDIC SURGEON. BC Orthopedic Surgeon needed for office practice in beautiful southern California area. Full- or part-time, surgery optional. Excellent compensation package. Send CV to Ronald Gilbert, MD, c/o Gilbert Medical Group, 1076 E. First St, #A, Tustin, CA 92680; or call (714) 832-1516.

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Western States OPENINGS

Many multispecialty groups and hospitals have asked us to recruit for over 300 positions of various specialties. Both permanent and locum tenens. Send CV to:

Western States Physician Services
5414 E. Montecito, Fresno, CA 93727
Or call 1 (800) 873-0786

STD FELLOWSHIP. One-year training program: clinical and epidemiologic aspects of sexually transmitted diseases. Available immediately. Jointly sponsored by UCSF/SF Department of Public Health. Send inquiries with CV to Infectious Diseases, SF General Hospital, 995 Potrero St, San Francisco, CA 94110. EO/AA employer M/F.

CRITICAL CARE MEDICINE. Four MDs BC both Internal Medicine and Critical Care Medicine seeking fifth associate with similar credentials in busy Critical Care Medicine practice. Central California city, over 500,000 population. Reply to Number 207, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

OCCUPATIONAL MEDICINE PHYSICIAN. BC is preferred, but will consider physician with a strong background in Occupational Medicine. Competitive salary and benefits. Located in an outstanding community, the Santa Clarita Valley. If you would like to continue to use your clinical skills, yet also be involved in administrative decisions, please submit your CV to Richard Kessler, Dir., Occup. Health Services, c/o SCV Healthcare Management Group, Valencia, CA 91355.

DIRECTOR OF EMERGENCY MEDICINE. Immediate opening for Director-Emergency Medicine. Salary plus incentives. Present volume, 6,000 visits annually. Please contact Mike R. Piper, Churchill Community Hospital, Fallon, NV; (702) 423-3151.

NORTHERN CALIFORNIA. Multispecialty group in central valley community 60 miles east of San Francisco seeks well-trained OB/GYN, Cardiologist, ENT, Pediatrician, and Neurologist. Growing community of 32,000 in rural-suburban setting offers reasonable housing costs, good schools, and nearby recreational areas. Ken Baker, PSG, 120 Montgomery St, Ste 710, San Francisco, CA 94104; (415) 399-8840.

SOUTHERN CALIFORNIA. Young Family Practitioner with dynamic practice seeking associate for future partnership. Generous salary/guarantee and incentives package. New medical office near outstanding 300-bed community hospital. Growing community within one hour of beaches and mountains. Ken Baker, PSG, 120 Montgomery St, Ste 710, San Francisco, CA 94104; (415) 399-8840.

BC/BE CARDIOLOGIST FULL-TIME. Community hospital in San Mateo, California. Mark L. Highman, MD, (415) 573-3786.

TWO NEUROSURGERY FELLOW VACANCIES. Position available July 1, 1990, for a Clinical and Research Neurosurgery Fellow at the new Los Angeles County/Olive View Medical Center, a teaching hospital for the UCLA School of Medicine, serving the San Fernando Valley. A California license is necessary. Excellent fringe benefits. Send CV and bibliography with letter of application to Donald Becker, MD, Chief, Division of Neurosurgery, UCLA School of Medicine, 10833 LeConte Ave, 74-140-CHS, Los Angeles, CA 90024-6901; (213) 825-5111, or Mario Ammirati, MD, Assistant Professor, Division of Neurosurgery, UCLA; Chief, Division of Neurosurgery, Olive View Medical Center, 14445 Olive View Dr, Sylmar, CA 91342; (818) 364-3194 or (213) 825-5111. Equal Opportunity Employer M/F.

NORTHERN CALIFORNIA, BC/BE Obstetrician/Gynecologist. 75 physician multispecialty group seeks partner. Good call coverage and referral pattern. $130K salary guarantee plus percentage. Paid malpractice, excellent benefits package. State-of-the-art equipment/facilities. Send CV or call Sharon Mac Kenzie, PO Box 1240, Trinidad, CA 95570; 1 (800) 735-4431.

CALIFORNIA
FAMILY PRACTICE
INTERNAL MEDICINE
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physicians to join Family Walk-In Medical Centers staff, a growing health care provider with five medical centers in Fresno, California, which is located in the Central San Joaquin Valley. Fresno metropolitan area has a population of over 400,000. Easy access to major metropolitan areas, Pacific coast and the Sierras. Salary guarantee of $100K to $120K for Family Practice, Internal Medicine, and Pediatric physicians; $150K for Surgeons, or equal to an average of the last two years' earnings, whichever is greater. Malpractice paid. Excellent working conditions. Contact **Juanita Perry, Human Resources Director, Family Walk-In Medical Centers, 1021 E. Herndon Ave, Fresno, CA 93710; (209) 449-6430**

SAN FRANCISCO PENINSULA. Well trained BC Internal Medicine, Family Practice, or Emergency room MD for busy Urgent Care Division of large, private, multispecialty group practice. Full- and part-time position available. Send CV to S. M. Stone, MD, Palo Alto Medical Foundation, 300 Homer Ave, Palo Alto, CA 94301.

LARGE SAN DIEGO MEDICAL GROUP with busy multisite Urgent Care Department has positions available for full-time career Urgent Care/Emergency Physicians. Excellent working conditions, competitive salary, benefits, and partnership opportunity. Part-time positions also available. Contact Betty Jones, Urgent Care Coordinator, Sharp Rees-Stealy Medical Group, 1963 4th Ave, San Diego, CA 92101; (619) 699-1578.

SEEKING ASSOCIATE WITH PARTNERSHIP OR TAKE-OVER POTENTIAL. Large, thriving practice in northern Central Valley of California. Excellent hospitals. Excellent compensation and benefits. Municipality of 200,000. Desirable climate, schools, colleges, and nearby resorts. Call (209) 474-3071.

ONCOLOGY—SEATTLE, WASHINGTON SUBURB. Hospital is seeking Oncologist for private practice. Excellent opportunity. For details, call Eloise Gusman, 1 (800) 535-7698 or send CV to PO Box 1685, Covington, LA 70434-1685.

The DEPARTMENT of PEDIATRIC HEMATOLOGY/ ONCOLOGY at VALLEY CHILDREN'S HOSPITAL

is seeking a second, full-time hospital-based Pediatric Hematologist/Oncologist. The candidate must be BC or BE in Pediatric Hematology/Oncology. Responsibilities include patient care, teaching, and clinical research.

Valley Children's Hospital is affiliated with the Children's Cancer Study Group and with the University of California, San Francisco, Fresno Pediatric Residency Program.

Please contact:

Stan Schofield
Assistant Vice President
Medical Affairs
Valley Children's Hospital
3151 N. Millbrook
Fresno, CA 93703

INTERNAL MEDICINE. BC/BE Internist. Excellent practice opportunity for General Internist. Located midway between Sacramento and San Francisco serving a rapidly growing community with a population of 70,000 plus. Office space in close proximity to new community hospital. Extremely attractive assistance package available. For further information please call or write Gary Stein, MD, 501 Nut Tree Ct, Vacaville, CA 95687; (707) 446-7100.

Medical Director

Yosemite Medical Clinic, a division of Samaritan Health Services, is an urgent care facility located in Yosemite National Park. We are seeking a Medical Director, MD or DO license required, with 2 years of administrative/management experience in addition to 2+ years in Emergency and Family practice. Proven record of effective interfacing with board members, community officials and physicians is essential. To inquire, call **1-800-395-0465**, or send resume to: **Samaritan Health Services, 1441 N. 12th St., Phoenix, AZ 85006.**

Equal Opportunity Employer

Samaritan Health Services

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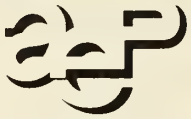

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Experienced Emergency Physicians with ACLS/ATLS certification needed to staff moderate volume Emergency Department located in San Francisco.

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Please contact: Nanette Peter, Recruitment Coordinator
(408) 293-8881

ENDOCRINOLOGIST/INTERNIST. Seeking BC/BE to join busy consultative and primary care practice of Endocrinology and Diabetology in desirable San Francisco bay area location. Group model HMO setting offers opportunities for teaching and clinical research. Competitive starting salary commensurate with experience. Outstanding benefit package including vacation, educational leave; life, health, disability, and malpractice insurance; and excellent retirement plan. For more information, please respond with CV to J. Mason, MD, Permanente Medical Group, 260 International Cir, Department WJM, San Jose, CA 95119; or call (408) 972-6428. EOE.

CENTRAL CALIFORNIA FAMILY PRACTICE/ GENERAL PRACTICE. We have an opening for a Family Practice Physician. Clinic is a 17,000 square foot primary care facility located near Bakersfield offering medical, dental, lab, x-ray, and pharmacy services. Excellent salary plus incentive, plus inpatient revenue and excellent benefit package. Call George Johnston (805) 845-3731 for details or write PO Box 457, Lamont, CA 93241.

GENERAL INTERNAL MEDICINE—NEVADA, CALIFORNIA, TEXAS, LOUISIANA, FLORIDA! Private practice opportunities available. For details, call Eloise Gusman, 1 (800) 535-7698 or send CV to PO Box 1685, Covington, LA 70434-1685.

PSYCHIATRIST FOR ROCKY MOUNTAIN CITY. An impressive Rocky Mountain community in Montana seeks Psychiatrist for well managed mental health clinic. Opportunity to succeed the present medical director exists within the next two to three years. Position includes both inpatient and outpatient practice and program development. Community population is over 80,000 with two modern hospitals. Liberal financial package offered. For more information call Jacquelin Walker, 1 (800) 776-7330, or write E. G. Todd Associates, 8600 Farley, Ste 100, Overland Park, KS 66212.

PSYCHIATRIST. Innovative team working with older adults. Med. evaluations, consultations, some supervision. $100K, plus benefits for full-time. Part-time also available. National Institute for Behavior Change, (303) 296-2244. Ask for Lois Munson.

AMBULATORY CARE, HAYWARD AND MODESTO. Thriving practices, attractive facilities. Competitive salary, profit-sharing, partnership, growth potential, paid malpractice. Contact Jane Dressler, California Emergency Physicians, 2101 Webster St, #1050, Oakland, CA 94612; (415) 835-7431. Outside of California, (800) 842-2619.

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Director

Catherine M. Dawson
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1-800-527-2145

EGSI, 1717 Main Street, Suite 5200
Dallas, Texas 75201
214/761-9200

ONCOLOGIST/HEMATOLOGIST, BC/BE to join busy established private practice in Los Angeles. First year guarantee with incentives. Position available fall, 1990. Please send CV to Number 213, Western Jounal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

INTERNAL MEDICINE/GERIATRIC—Looking for a primary care position with challenging and appreciative patients, quality associates, tolerable schedules in an attractive community? Send CV to Julie A. Prazich, MD, Medical Director, Sharp Senior HealthCare, 3545 Fourth Ave, San Diego, CA 92103.

ASSOCIATE IN PEDIATRICS. Kern Medical Center, Bakersfield, California, a teaching hospital affiliated with UCLA and UCI Schools of Medicine, seeks an Associate in the Division of Pediatrics. Prerequisites include eligibility or certification by the American Board of Pediatrics, strong interest in teaching, and qualifications for faculty appointment in UCLA Department of Pediatrics. Comprehensive salary and benefit package. A part-time private practice is permitted. Medical center is in central California, a mid-sized urban community with moderate cost of living. Send CV and inquiries to Navin Amin, MD, Chairman, Department of Family Practice/Pediatrics, Kern Medical Center, 1830 Flower St, Bakersfield, CA 93305.

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ROCKWOOD CLINIC, P.S.—a network of Family Practice clinics (main building and six satellites) seeks BE/BC Family Practitioners to join these busy independent practices offering the full range of inpatient/ outpatient services, including obstetrics. ADVANTAGES INCLUDE:

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CONTACT:
Colleen Mooney
Recruitment Coordinator
Rockwood Clinic
E. 400 Fifth Ave
Spokane, WA 99202
(509) 838-2531

NORTHERN CALIFORNIA—SAN FRANCISCO BAY AREA. Leading HMO is seeking BC/BE physician to staff a busy, urban, full-service Emergency Department with the possibility of administrative advancement. Kaiser Permanente is a large pre-paid HMO offering competitive salary, job security, shareholder status, and generous benefits including health care, life insurance, disability insurance, sick leave, mortgage assistance, and educational leave. Please address all inquiries to David Witt, MD, Emergency Department, Kaiser Permanente Medical Center, 1200 El Camino Real, AD-WJM, South San Francisco, CA 94080-3299; or call (415) 742-2516. EOE.

WASHINGTON STATE. 31 physician, multispecialty group is recruiting a BC/BE Family Physician for a 40-hour per week position in our clinic-based Immediate Care Center. Attractive salary and benefit package. No evening call or hospital commitment. Attractive farming and college community of 35,000 in southeastern Washington State. Inquiries and CV to Robert G. Caudill, MD, Walla Walla Clinic, 55 W. Tietan, Walla Walla, WA 99362; (509) 525-3720, ext 285.

INTERNIST, BC/BE to join busy Primary Care/ Cardiology practice in San Diego/La Jolla area. Excellent working environment, guaranteed income and partnership for right individual. Please send CV to J. Simmons, Mission Bay Hospital, 3030 Bunker Hill St, San Diego, CA 92109.

(Continued on Page 106)

The Permanente Medical Group, Inc.
Northern California

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The Permanente Medical Group, Inc., the largest multispecialty group practice in the U.S., is undergoing explosive growth in its Northern California region: the San Francisco Bay Area, Sacramento and the Central Valley. Our rapid increase in membership has created practice opportunities throughout the region.

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TPMG offers many benefits: scheduled time off with cross-coverage provided by your colleagues, continuing education, malpractice insurance, a substantial retirement program and special arrangements for physicians transferring from established practice. For complete information, call or send CV to: The Permanente Medical Group, Inc., Richmond Prescott, M.D., Physician Recruitment Services, Dept. WJM-9240, 1814 Franklin, 4th Floor, Oakland, CA 94612. (800) 777-4912. Equal Opportunity Employer.

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(Continued from Page 104)

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STAFF PHYSICIAN. Join us in providing comprehensive medical care for 330 developmentally disabled children and adults at the Wyoming State Training school. Three physicians and one physician's assistant staff our 18-bed health care center and provide medical support to nursing, therapists, professional and paraprofessional staff across campus. Good working relationships with excellent hospital and medical group in local community. Progressive habilitation-oriented working environment. Attractive benefits, malpractice insurance provided, no overhead. Annual salary range $50,000 to $70,000 depending upon experience and qualifications. Campus situated in pleasant west-central Wyoming community of Lander, minutes from beautiful Wind River Mountain Range and close to Yellowstone and Grand Teton National Parks. Outstanding hiking, fishing, hunting, skiing, wilderness areas nearby. Good schools and services, low cost of living, no state income tax. Contact Director of Clinical Services, Wyoming State Training School, 8204 State Highway 789, Lander, WY 82520; or call (307) 332-5302. Equal Opportunity Employer.

MARYSVILLE (YUBA CITY). Primary care provider. Northern California primary care clinic with large Medi-Cal clientele. Three physicians, two physician assistants. No OB. No surgery. Near mountains, close to Sacramento, 2½ hours to Lake Tahoe and San Francisco. Salary $86,113 plus. Please contact Ed Allen, 938 14th St, Marysville, CA 95901; or call (916) 741-6244.

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Attn: Administration
Kaiser Permanente Medical Center
27400 Hesperian Blvd
Hayward, CA 94545
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ORTHOPEDIC SURGEONS, BC/BE sought for expanding group in Sacramento. Currently seeking experienced hand/upper extremity, spine, and general Orthopedists. Excellent growth and compensation potential. Limited call schedule, flexible hours, med/legal evaluations. Send CV to Number 214, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

SACRAMENTO, CALIFORNIA. Two Occupational Medicine Physicians needed for urgent care clinics. Unique opportunity with no on-call or weekend hours. BE/BC in Occupational Medicine preferred but will consider Emergency Room, Internal Medicine, or Family Practice background. Compensation, benefits, and hours are negotiable. Positions are associated with an established multispecialist group. Excellent locale, affordable housing, quality support personnel, and equity position in the group is possible. Send CV to John Murphy, PHC Administration, 8110 Timberlake Way, Ste D, Sacramento, CA 95823.

MEDICAL DIRECTOR. HEALS, the personal care physician Health Plan, is a popular northern California IPA HMO with over 95,000 members located in a key metropolitan market. We are currently at a pivotal point in our evolution and can offer an exciting opportunity for strategic development! Medical Director will serve as liaison to 1,200 member IPA. Will manage all areas of physician relations, utilization, and quality issues. Ideal candidate will have minimum five years private practice or Medical Director experience and understand, practice, and support the managed care concept. Direct CV with compensation requirements to Professional Staffing, HEALS Health Plan, 155 Grand Ave, Oakland, CA 94612.

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Dynamic 55 physician multispecialty group with seven locations seeks BC/BE physicians in the following specialties: Family Practice, Geriatrics, Occupational Medicine, Orthopedics, Psychiatry, Urgency Care, Urology. Eugene, attractive university town within 60 mile radius of Cascade Mountains and Oregon coast, offers superlative life-style, fine school system, active and varied cultural opportunities, and unlimited recreation. Qualified candidates send CV and three letters of reference to:

Physician Recruiter
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NEUROLOGIST for multispecialty pain treatment center in San Diego. Work with Orthopedist, Physical Therapist, Psychiatrist. Established 1977. CV to K. Shandell, MD, 1075 Camino del Rio S, San Diego, CA 92108.

SAN FRANCISCO BAY AREA—General Internist. Energetic BC/BE General Internist needed immediately for nine MD Fremont satellite of Palo Alto Medical Clinic. Broad inpatient/outpatient Internal Medicine practice in growing bay area community. Excellent location for family with convenient access to San Francisco. Please send CV to David Hooper, MD, PAMC, Fremont Center, 39500 Liberty St, Fremont, CA 94538.

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(Continued on Page 107)

(Continued from Page 106)

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San Francisco, CA 94120-7602

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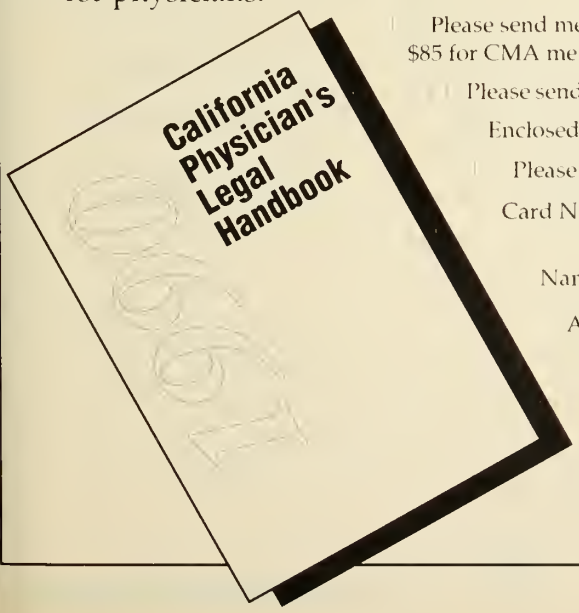

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(415) 882-5175

(Continued on Page 108)

(Continued from Page 107)

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Northern and central California. Dermatology, Family, Gastroenterology, GYN, Internal Medicine, Ophthalmology, Orthopedics, Otolaryngology, Pediatrics, Personal Injury, and Plastic Surgery. Contact: **Bradshaw Asociates, 21 Altamount, Orinda, CA 94563; (415) 376-0762, FAX (415) 376-0813.**

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SAN DIEGO COUNTY. Cardiology, Internal, OB/GYN and Pediatric practices available. Long established—doctors retiring. Various prices and low down payments. Call CBI, San Diego County's professional practice sales specialists, (619) 283-7009.

SAN DIEGO NORTH COUNTY. Ambulatory Care Family Practice/Occupational Medical Center. Gross $475,000. Well located, attractive, fully equipped 2,700 square foot office. Open 8:00 am to 8:00 pm, 7 days per week. Contact Practice Consultants, Dr Bernard Press, Broker, (619) 528-2321.

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SAN FRANCISCO BAY AREA. Pain management practice. Excellent staff and administration. Opportunity for Internist, Psychiatrist, Family Practitioner, Neurologist, or partnership interested in pain or psychosomatic medicine. Reply to Number 208, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

FAMILY PRACTICE, BERKELEY, CALIFORNIA. Growing established practice in beautiful San Francisco bay area shared with one associate. Modest buy-in. (415) 843-4544.

CALIFORNIA RADIOLOGY. Well established Diagnostic Radiology practice is available in Sacramento. General and mammography. Annual collections $550,000 plus. Call or write John Harrison, Practice Dynamics, 11222 Richmond, Ste 125, Houston, TX 77082; 1 (800) 933-0911.

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SALT LAKE CITY, UTAH. Internal Medicine Practice—Office Condominium—for sale. Space for Pharmacy or second professional. On public transportation. Parking. Excellent living. Call (801) 355-3822.

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PHYSICIAN OPENING. Small suite to be vacated soon. Building has adjacent physician, specialist, dentist. Great place for young practice. Red Bluff, California; (916) 527-2877.

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GENERAL INTERNIST—BC seeks locum tenens positions in Hawaii. Full- or part-time. Experienced in Primary Care, Emergency Medicine, and inpatient/ICU care. Reply to Number 210, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

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SPECIAL ISSUES

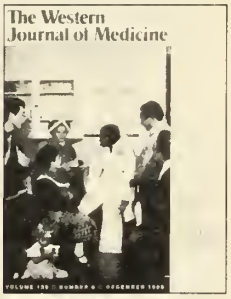
Addiction Medicine
and the Primary Care Physician

Addiction Medicine and the Primary Care Physician was conceived to be part of the initiative to expand the involvement of all specialties of medicine in the prevention and treatment of addictive disease. Topics covered include chemical dependence and the workplace, alcoholism, methadone maintenance in the treatment of opioid dependence, nicotine dependence, and treatment of cocaine dependence. David Smith MD, Special Editor, 1990.

Women and Medicine

This special issue explores both the professional side of women in medicine and the diagnosis and treatment of women patients. Topics covered include liver disease, women and AIDS, heart disease, hysterectomy, PMS, ovarian cancer, and women physicians and organized medicine. Linda Hawes Clever, MD, Special Issue Editor, 1988.

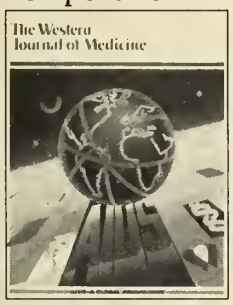
Cross-cultural Medicine



Cross-cultural medicine is devoted to the care of patients of different cultural, ethnic, or religious backgrounds. Subjects include Southeast Asian refugees in the American health care system, psychiatry and Chinese culture, health and illness in Filipino immigrants, and health care of Middle Eastern patients. M. Margaret Clark, PhD, Special Issue Editor, 1983. 2nd reprinted edition.

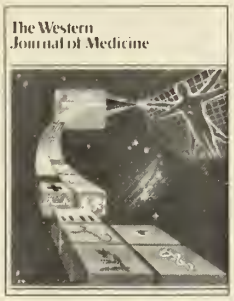
Also available:

AIDS—A Global Perspective



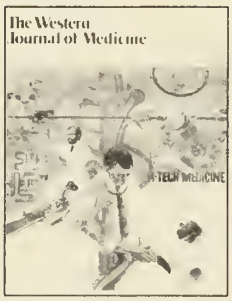
Jonathan M. Mann, MD
Special Issue Editor, 1987

Medical Informatics



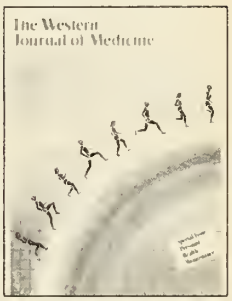
Marsden S. Blois, MD
Special Issue Editor, 1986

High-Tech Medicine



R. Paul Robertson, MD
Special Issue Editor, 1985

Personal Health Maintenance



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WJ7/90

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Alaska State Medical Association—2401 E 42nd Ave, Suite 104, Anchorage 99508. (907) 562-2662. Annual Meeting: 1991, date and location to be announced.

Arizona Medical Association, Inc—810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: 1991, date and location to be announced.

California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 3-8, 1991, Bally's Grand Hotel, Reno.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 13-16, 1990, Keystone.

Hawaii Medical Association—1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: October 12-14, 1990, Ilikai, Honolulu.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 26-28, 1990, Sun Valley.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 4-6, 1990, Sheraton, Billings.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: 1991, date and location to be announced.

New Mexico Medical Society—7770 Jefferson, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: 1991, date and location to be announced.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting (House of Delegates only): 1991, date and location to be announced.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 12-14, 1990, Marriott Hotel, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: September 20-23, 1990, Sheraton, Spokane.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: 1991, date and location to be announced.

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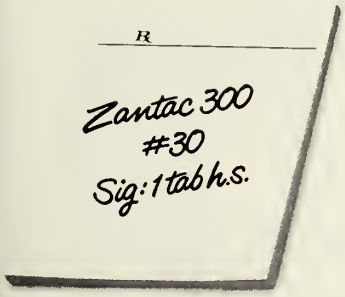
In active duodenal ulcers

Once-a-night h.s. therapy controls acid rain

Zantac® 300
ranitidine HCl/Glaxo 300 mg tablets



ZANTAC® 150 Tablets
(ranitidine hydrochloride)
ZANTAC® 300 Tablets
(ranitidine hydrochloride)

BRIEF SUMMARY

The following is a brief summary only. Before prescribing, see complete prescribing information in ZANTAC® product labeling.

INDICATIONS AND USAGE: ZANTAC® is indicated in:
1. Short-term treatment of **active duodenal ulcer**. Most patients heal within four weeks.
2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathological hypersecretory conditions** (eg, Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of **active, benign gastric ulcer**. Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated.
5. Treatment of **gastroesophageal reflux disease (GERD)**. Symptomatic relief commonly occurs within one or two weeks after starting therapy. Therapy for longer than six weeks has not been studied.

In active duodenal ulcer; active, benign gastric ulcer; hypersecretory states; and GERD, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: ZANTAC® is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS: General: 1. Symptomatic response to ZANTAC® therapy does not preclude the presence of gastric malignancy.
2. Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see **DOSAGE AND ADMINISTRATION**). Caution should be observed in patients with hepatic dysfunction since ZANTAC is metabolized in the liver.

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during ZANTAC therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although ZANTAC has been reported to bind weakly to cytochrome P-450 in vitro, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions which suggest that ZANTAC may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2,000 mg/kg/day.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella*, *E coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ZANTAC. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: ZANTAC is secreted in human milk. Caution should be exercised when ZANTAC is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with oral ZANTAC®. The relationship to ZANTAC therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to ZANTAC administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported.

Cardiovascular: Rare reports of tachycardia, bradycardia, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, and abdominal discomfort/pain.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid IV for seven days, and in 4 of 24 subjects receiving 50 mg qid IV for five days. With oral administration there have been occasional reports of reversible hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice.

Musculoskeletal: Rare reports of arthralgias.

Hematologic: Reversible blood count changes (leukopenia, granulocytopenia, thrombocytopenia) have occurred in a few patients. Rare cases of agranulocytosis or of pancytopenia, sometimes with marrow hypoplasia, have been reported.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by ZANTAC® (ranitidine hydrochloride) and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when ZANTAC has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving ZANTAC, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia) and small increases in serum creatinine.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg twice daily. An alternate dosage of 300 mg once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.

Maintenance Therapy: The current recommended adult oral dosage is 150 mg at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg twice a day. In some patients it may be necessary to administer ZANTAC® 150-mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/day have been employed in patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg twice a day.

GERD: The current recommended adult oral dosage is 150 mg twice a day.

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with ZANTAC, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: ZANTAC® 300 Tablets (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 (NDC 0173-0393-40) and unit dose packs of 100 tablets (NDC 0173-0393-47).

ZANTAC® 150 Tablets (ranitidine hydrochloride equivalent to 150 mg of ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 60 tablets (NDC 0173-0344-42) and unit dose packs of 100 tablets (NDC 0173-0344-47).

Store between 15° and 30°C (59° and 86°F) in a dry place. Protect from light. Replace cap securely after each opening.

August 1987

Glaxo

Glaxo Inc.
Research Triangle Park, NC 27709

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CONTROL ACID RAIN

with once-a-night h.s. therapy for active duodenal ulcers

Zantac® 300

ranitidine HCl/Glaxo 300 mg tablets

Glaxo ROCHE

See adjacent page for Brief Summary of Product Information

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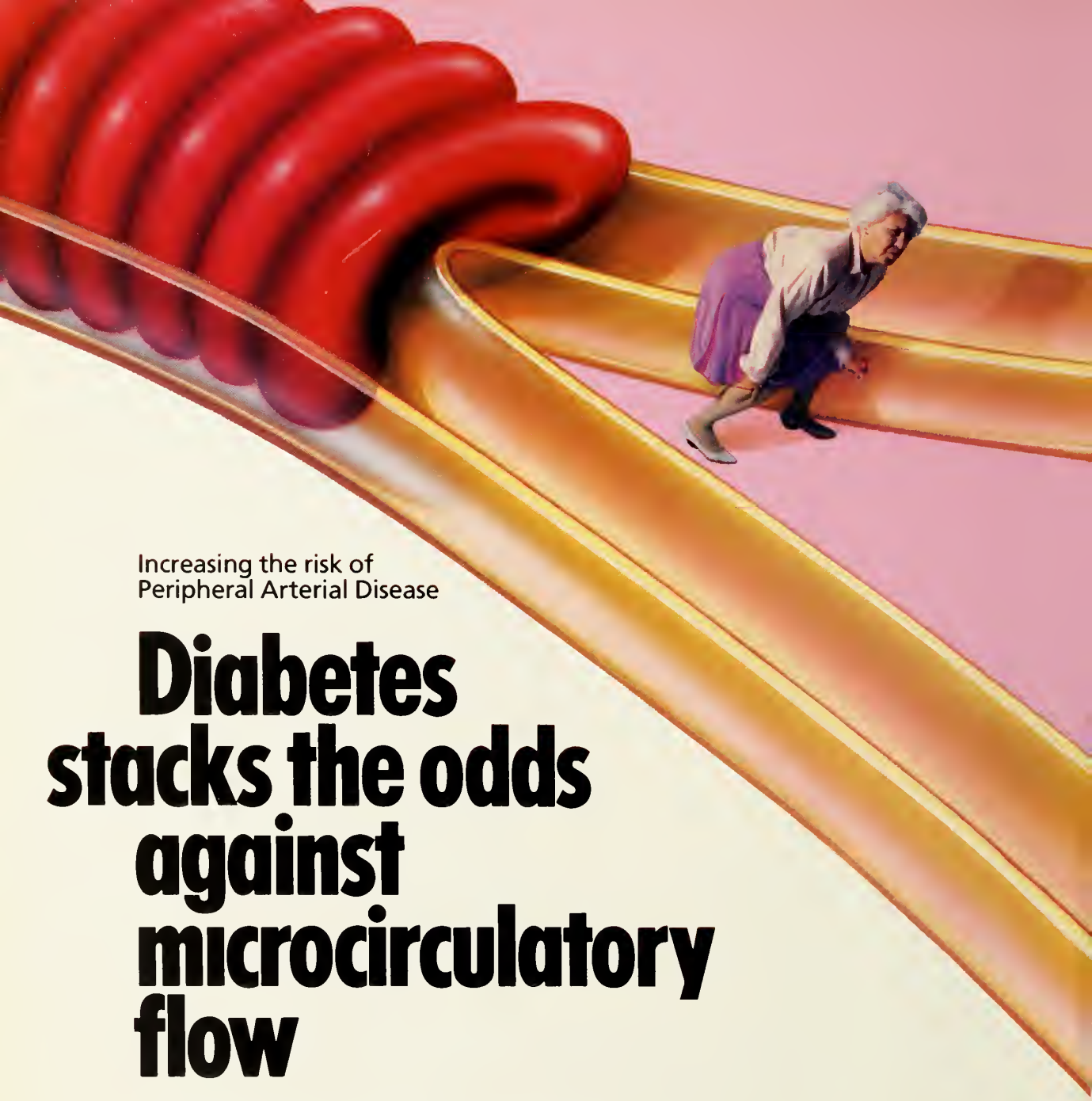
Official Journal of the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology



Increasing the risk of
Peripheral Arterial Disease

Diabetes stacks the odds against microcirculatory flow

In diabetes, atherosclerotic changes occur above *and* below the knee, often involving smaller vessels and multisegmental occlusions.[1] Diabetes has also been *associated* with decreased red cell flexibility, and increasing fibrinogen levels, platelet aggregation and platelet adherence, factors which predispose patients to peripheral arterial disease.[1]

Duration of Diabetes	Incidence of PAD
10 years	15%
20 years	45%

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Now Medi-Cal approved
for patients with diabetes who have been diagnosed as having intermittent claudication
Drug Type Code: 5041AHE

Trental® improves microcirculatory flow and lifestyle for many diabetics with PAD

Trental® (pentoxifylline) increases red cell flexibility[2] while decreasing elevated plasma fibrinogen levels,[3] aggregation of platelets[4] and red cells.[5] The resulting increase in microcirculatory flow enhances tissue perfusion and oxygenation.[6]

With Trental, patients experience significant improvement in pain-free walking distance, paresthesia, skin temperature and subjective overall response.[7]

Not a vasodilator • Not an anticoagulant • Not related to aspirin or dipyridamole

Trental® 400 mg Tablets
(pentoxifylline)

The only proven-effective agent for intermittent claudication, a symptom of peripheral arterial disease

Please see references and brief summary of prescribing information on following page.

Trental® can improve function and symptoms, but is not intended to replace more definitive therapy, such as surgery.

References:
1. Levin ME, Sicard GA: Evaluating and treating diabetic peripheral vascular disease, Part I. *Clinical Diabetes* May/Jun 1987. **2.** Stormer B, Kleinschmidt K, Loose D, et al: Rheological changes in the blood of patients with chronic arterial occlusive disease after the administration of vasoactive drugs. *Curr Med Res Opin* 1977;4:588-595. **3.** Perego MA, Sergio G, Artale F: Haemorrheological aspects of the pathophysiology and clinical features of peripheral occlusive arterial disease. *Pharmatherapeutica* 1983;3(1):91. **4.** Seiffge D: *IRCS Med Sci* 1980;8:727. **5.** Lowe GDO, Drummond MM, Forbes CD, et al: Blood and plasma viscosity in prediction of venous thrombosis. Abstracts: 77, International Symposium on Filterability and Red Blood Cell Deformability, Göteborg, Sweden, Sep 11-13, 1980. **6.** Ehrly AM: Effects of orally administered pentoxifylline on muscular oxygen pressure in patients with intermittent claudication. *IRCS Med Sci* 1982;10:401. **7.** Schubotz R: Double-blind trial of pentoxifylline in diabetes with peripheral vascular disorders. *Pharmatherapeutica* 1976;1(3):172-179.

Trental® (pentoxifylline) Tablets, 400 mg
A brief summary of the Prescribing Information follows.

INDICATIONS AND USAGE:
Trental® (pentoxifylline) is indicated for the treatment of patients with intermittent claudication on the basis of chronic occlusive arterial disease of the limbs. Trental® (pentoxifylline) can improve function and symptoms but is not intended to replace more definitive therapy, such as surgical bypass, or removal of arterial obstructions when treating peripheral vascular disease.

CONTRAINDICATIONS:
Trental® (pentoxifylline) should not be used in patients who have previously exhibited intolerance to this product or methylxanthines such as caffeine, theophylline, and theobromine.

PRECAUTIONS:
General: Patients with chronic occlusive arterial disease of the limbs frequently show other manifestations of arteriosclerotic disease. Trental® (pentoxifylline) has been used safely for treatment of peripheral arterial disease in patients with concurrent coronary artery and cerebrovascular diseases, but there have been occasional reports of angina, hypotension, and arrhythmia. Controlled trials do not show that Trental® (pentoxifylline) causes such adverse effects more often than placebo, but, as it is a methylxanthine derivative, it is possible some individuals will experience such responses.
Drug Interactions: Although a causal relationship has not been established, there have been reports of bleeding and/or prolonged prothrombin time in patients treated with Trental® (pentoxifylline) with and without anticoagulants or platelet aggregation inhibitors. Patients on warfarin should have more frequent monitoring of prothrombin times, while patients with other risk factors complicated by hemorrhage (e.g., recent surgery, peptic ulceration) should have periodic examinations for bleeding including hematocrit and/or hemoglobin. Trental® (pentoxifylline) has been used concurrently with antihypertensive drugs, beta blockers, digitalis, diuretics, antidiabetic agents, and antiarrhythmics, without observed problems. Small decreases in blood pressure have been observed in some patients treated with Trental® (pentoxifylline); periodic systemic blood pressure monitoring is recommended for patients receiving concomitant antihypertensive therapy. If indicated, dosage of the antihypertensive agents should be reduced.
Carcinogenesis, Mutagenesis and Impairment of Fertility: Long-term studies of the carcinogenic potential of pentoxifylline were conducted in mice and rats by dietary administration of the drug at doses up to approximately 24 times (570 mg/kg) the maximum recommended human daily dose (MRHD) of 24 mg/kg for 18 months in mice and 18 months in rats with an additional 6 months without drug exposure in the latter. No carcinogenic potential for pentoxifylline was noted in the mouse study. In the rat study, there was a statistically significant increase in benign mammary fibroadenomas in females in the high dose group (24 x MRHD). The relevance of this finding to human use is uncertain since this was only a marginal statistically significant increase for a tumor that is common in aged rats. Pentoxifylline was devoid of mutagenic activity in various strains of *Salmonella* (Ames test) when tested in the presence and absence of metabolic activation.
Pregnancy: Category C. Teratogenic studies have been performed in rats and rabbits at oral doses up to about 25 and 10 times the maximum recommended human daily dose (MRHD) of 24 mg/kg, respectively. No evidence of fetal malformation was observed. Increased resorption was seen in rats at 25 times MRHD. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Trental® (pentoxifylline) should be used during pregnancy only if clearly needed.
Nursing Mothers: Pentoxifylline and its metabolites are excreted in human milk. Because of the potential for tumorigenicity shown for pentoxifylline in rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.
Pediatric Use: Safety and effectiveness in children below the age of 18 years have not been established.

ADVERSE REACTIONS:
Clinical trials were conducted using either controlled-release Trental® (pentoxifylline) tablets for up to 60 weeks or immediate-release Trental® (pentoxifylline) capsules for up to 24 weeks. Dosage ranges in the tablet studies were 400 mg bid to tid and in the capsule studies, 200-400 mg tid.
The table summarizes the incidence (in percent) of adverse reactions considered drug related, as well as the numbers of patients who received controlled-release Trental® (pentoxifylline) tablets, immediate-release Trental® (pentoxifylline) capsules, or the corresponding placebos. The incidence of adverse reactions was higher in the capsule studies (where dose related increases were seen in digestive and nervous system side effects) than in the tablet studies. Studies with the capsule include domestic experience, whereas studies with the controlled-release tablets were conducted outside the U.S. The table indicates that in the tablet studies few patients discontinued because of adverse effects.

INCIDENCE (%) OF SIDE EFFECTS

	Controlled-Release Tablets		Immediate-Release Capsules	
	Commercially Available		Used only for Controlled Clinical Trials	
	Trental®	Placebo	Trental®	Placebo
(Numbers of Patients at Risk)	(321)	(128)	(177)	(138)
Discontinued for Side Effect	3.1	0	9.6	7.2
CARDIOVASCULAR SYSTEM				
Angina/Chest Pain	0.3	—	1.1	2.2
Arrhythmia/Palpitation	—	—	1.7	0.7
Flushing	—	—	2.3	0.7
DIGESTIVE SYSTEM				
Abdominal Discomfort	—	—	4.0	1.4
Belching/Flatus/Bloating	0.6	—	9.0	3.6
Diarrhea	—	—	3.4	2.9
Dyspepsia	2.8	4.7	9.6	2.9
Nausea	2.2	0.8	28.8	8.7
Vomiting	1.2	—	4.5	0.7
NERVOUS SYSTEM				
Agitation/Nervousness	—	—	1.7	0.7
Dizziness	1.9	3.1	11.9	4.3
Drowsiness	—	—	1.1	5.8
Headache	1.2	1.6	6.2	5.8
Insomnia	—	—	2.3	2.2
Tremor	0.3	0.8	—	—
Blurred Vision	—	—	2.3	1.4

Trental® (pentoxifylline) has been marketed in Europe and elsewhere since 1972. In addition to the above symptoms, the following have been reported spontaneously since marketing or occurred in other clinical trials with an incidence of less than 1%; the causal relationship was uncertain:
Cardiovascular—dyspnea, edema, hypotension.
Digestive—anorexia, cholecystitis, constipation, dry mouth/thirst.
Nervous—anxiety, confusion.
Respiratory—epistaxis, flu-like symptoms, laryngitis, nasal congestion.
Skin and Appendages—brittle fingernails, pruritus, rash, urticaria, angioedema.
Special Senses—blurred vision, conjunctivitis, earache, scotoma.
Miscellaneous—bad taste, excessive salivation, leukopenia, malaise, sore throat/swollen neck glands, weight change.
A few rare events have been reported spontaneously worldwide since marketing in 1972. Although they occurred under circumstances in which a causal relationship with pentoxifylline could not be established, they are listed to serve as information for physicians: Cardiovascular—angina, arrhythmia, tachycardia; Digestive—hepatitis, jaundice, increased liver enzymes; and Hemic and Lymphatic—decreased serum fibrinogen, pancytopenia, aplastic anemia, purpura, thrombocytopenia.

OVERDOSAGE:
Overdosage with Trental® (pentoxifylline) has been reported in children and adults. Symptoms appear to be dose related. A report from a poison control center on 44 patients taking overdoses of enteric-coated pentoxifylline tablets noted that symptoms usually occurred 4-5 hours after ingestion and lasted about 12 hours. The highest amount ingested was 80 mg/kg; flushing, hypotension, convulsions, somnolence, loss of consciousness, fever, and agitation occurred. All patients recovered.
In addition to symptomatic treatment and gastric lavage, special attention must be given to supporting respiration, maintaining systemic blood pressure, and controlling convulsions. Activated charcoal has been used to adsorb pentoxifylline in patients who have overdosed.

DOSAGE AND ADMINISTRATION:
The usual dosage of Trental® (pentoxifylline) in controlled-release tablet form is one tablet (400 mg) three times a day with meals.
While the effect of Trental® (pentoxifylline) may be seen within 2 to 4 weeks, it is recommended that treatment be continued for at least 8 weeks. Efficacy has been demonstrated in double-blind clinical studies of 6 months duration.
Digestive and central nervous system side effects are dose related. If patients develop these side effects it is recommended that the dosage be lowered to one tablet twice a day (800 mg/day). If side effects persist at this lower dosage, the administration of Trental® (pentoxifylline) should be discontinued. Edition 2/88
Trental® REG TM HOECHST AG

Hoechst-Roussel Pharmaceuticals Inc.
Somerville, New Jersey 08876-1258

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Help your patients take a step toward early detection and treatment of P.A.D....

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Name

Address

City State Zip

Cut out and mail to: Step Lively, HOECHST-ROUSSEL PHARMACEUTICALS INC., P.O. Box 831, Andover, New Jersey 07821

Trental® 400 mg Tablets
(pentoxifylline)

The only proven-effective agent for intermittent claudication, a symptom of peripheral arterial disease

Q73224-790

The results are worth waiting for.

Patience pays off when you start a patient on Trental®

Trental® therapy can make a dramatic difference to your patients – increasing their mobility and independence, enhancing their participation in social and professional activities, and giving them a fresh outlook on life. But, the physical improvement behind these benefits doesn't happen overnight. It's a gradual process.

3x3=success with Trental® treatment

To start patients off on the right foot with Trental®, follow the 3×3 formula for success.

3 tablets a day, with meals

The usual dosage of Trental® is one 400 mg tablet taken 3 times a day, with a full meal.

3-month initial trial, evaluate, then continue

While patients might feel somewhat better within weeks, at least 3 months' therapy is generally required before the full effectiveness of Trental® becomes evident. To sustain improvement, therapy must be continued.

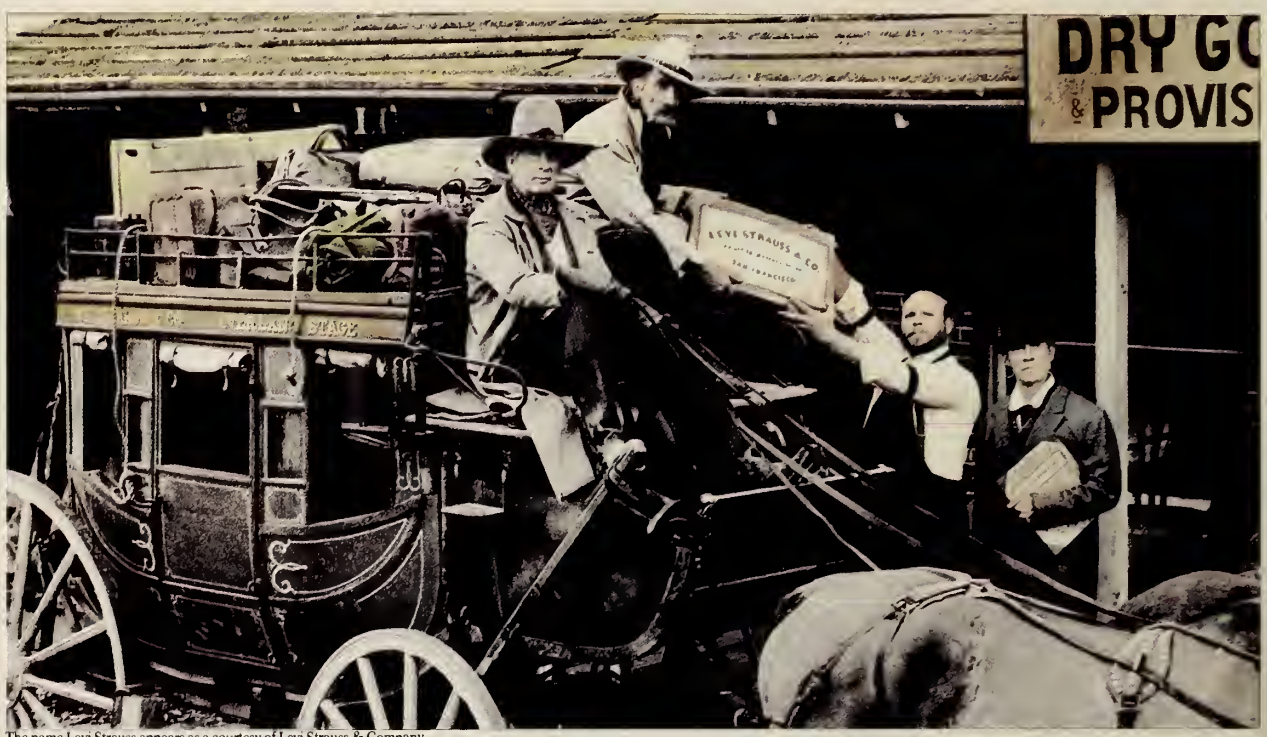
Trental® 400 mg Tablets

(pentoxifylline)

The only proven-effective agent for intermittent claudication—a symptom of peripheral arterial disease

Wells Fargo Comes Through

Then.



The name Levi Strauss appears as a courtesy of Levi Strauss & Company.

In early California, it took more than good intentions for small business to survive.

Often it took the resources and personal service of a Wells Fargo agent. If, for example, a merchant ran out of work pants, our agent could refer him to a gentleman named Levi Strauss who was always ready to fill an order for those copper-riveted denim pants.

The agent would even wire the order and see that it arrived promptly by Wells Fargo Express.

Today our agents are called Wells Fargo Business Bankers.™ And they're still coming through for every Wells Fargo small business customer.

Your Business Banker can provide access to financial resources that go far beyond those of less substantial banks. Including a wide range of financial products specifically designed for California small business. (After all, you've got enough to do without worrying about merchant cards and lines of credit and payroll and retirement programs.)

Along with the expertise of a banker who'll be there whenever you have a problem to solve or opportunity to profit from, you'll enjoy proven 24-hour person-to-person phone service. Plus longer, more convenient office hours to meet the needs of small business. Even on Saturdays.

If you'd like to sit down with a Wells Fargo Business Banker, simply call our Business Banking Hotline at 1-800-642-BANK, ext. 504. Let us know when it would be convenient for you.

Or talk to your local Wells Fargo office.

Wells Fargo comes through again.

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"We had loans all over town. Our Business Banker advised one loan, one line, one bank. A simple solution that saved us lots of headaches." *D. & L. Fullerton, Action Fire Protection, Stanton.*

"Talk about above and beyond the call of duty...the day after a major earthquake, our Business Banker still got our payroll processed!" *M. O'Brien, Cricklewood Restaurant, Santa Rosa.*

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BRIAN T. ANDREWS, MD; JAMES J. HERSHON, MD; PHILIP CALANCHINI, MD; G. JAMES AVERY II, MD; and J. DONALD HILL, MD

From the Departments of Neurological Surgery, Medicine, Cardiovascular Surgery, and Neurology, Pacific Presbyterian Medical Center, San Francisco.

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HILDY B. MEYERS, MD, MPH; SUSAN G. ZEPEDA, PhD; and MARGIE A. MURDOCK, RN, MSN

From the Division of Health Promotion and Disease Prevention and Alcohol Programs, County of Orange Health Care Agency, Santa Ana, and the Trauma Service, University of California, Irvine, Medical Center, Orange, California.

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WAYNE X. SHANDERA, MD

From the Division of General Internal Medicine, Baylor College of Medicine, Houston.

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ANNA M. FAN, PhD, and KENNETH W. KIZER, MD, MPH

From the Pesticide, Food, and Water Toxicology Unit, Hazard Evaluation Section, California Department of Health Services, Berkeley, and the California Department of Health Services, Sacramento.

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THOMAS W. WILSON, MD, MSc, FRCP(C); RAVI D. KAUSHAL, MBBS, MSc; and MERNE DUBOIS, RN

From the Departments of Pharmacology and Medicine, University of Saskatchewan College of Medicine, Saskatoon.

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For Brief Summary, please see following page.

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References: 1. Newton RE, *et al* A review of the side effect profile of buspirone *Am J Med* 1986;80(3B) 17-21 2. Lucki I, *et al* Differential effects of the anxiolytic drugs, diazepam and buspirone, on memory function *Br J Clin Pharmacol* 1987;23 207-211 3. Lader M Assessing the potential for buspirone dependence or abuse and effects of its withdrawal *Am J Med* 1987;82(5A) 20-26

Contraindications: Hypersensitivity to buspirone hydrochloride

Warnings: The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. Since blood pressure has become elevated when BuSpar was administered concomitantly with an MAOI, such concomitant use is not recommended BuSpar should not be employed in lieu of appropriate antipsychotic treatment.

Precautions: ***General***—*Interference with cognitive and motor performance:* Although buspirone is less sedating than other anxiolytics and does not produce significant functional impairment, its CNS effects in a given patient may not be predictable, therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone does not affect them adversely Although buspirone has not been shown to increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use with alcohol.

Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug dependent patients. Because buspirone will not block the withdrawal syndrome often seen with cessation of therapy with benzodiazepines and other common sedative/hypnotic drugs, before starting buspirone withdraw patients gradually from their prior treatment, especially those who used a CNS depressant chronically Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug and its elimination half-life The withdrawal syndrome can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

Possible concerns related to buspirone's binding to dopamine receptors: Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (eg, dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported, the syndrome may be due to increased central noradrenergic activity or may be attributable to dopaminergic effects (ie, represent akathisia).

Information for Patients—Patients should be instructed to inform their physician about any medications, prescription or nonprescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone, to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone, to inform their physician if they are breast feeding; and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them

Drug Interactions—Concomitant use with other CNS active drugs should be approached with caution (see **Warnings**). Concomitant use with trazodone may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients Concomitant administration of BuSpar and haloperidol resulted in increased serum haloperidol concentrations in normal volunteers The clinical significance is not clear. Buspirone does not displace tightly bound drugs like phenytoin, propranolol, and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin However, there was one report of prolonged prothrombin time when buspirone was given to a patient also treated with warfarin, phenytoin, phenobarbital, digoxin, and Synthroid

Carcinogenesis, Mutagenesis, Impairment of Fertility—No evidence of carcinogenic potential was observed in rats or mice, buspirone did not induce point mutations, nor was DNA damage observed, chromosomal aberrations or abnormalities did not occur

Pregnancy: Teratogenic Effects—Pregnancy Category B Should be used during pregnancy only if clearly needed

Nursing Mothers—Administration to nursing women should be avoided if clinically possible

Pediatric Use—The safety and effectiveness have not been determined in individuals below 18 years of age

Use in the Elderly—No unusual, adverse, age-related phenomena have been identified in elderly patients receiving a total, modal daily dose of 15 mg

Use in Patients with Impaired Hepatic or Renal Function—Since buspirone is metabolized by the liver and excreted by the kidneys, it is not recommended in severe hepatic or renal impairment

Adverse Reactions (See also Precautions): ***Commonly Observed***—The more commonly observed untoward events, not seen at an equivalent incidence in placebo-treated patients, include dizziness, nausea, headache, nervousness, lightheadedness, and excitement.

Associated with Discontinuation of Treatment—The more common events causing discontinuation included central nervous system disturbances (3 4%), primarily dizziness, insomnia, nervousness, drowsiness, lightheaded feeling, gastrointestinal disturbances (1.2%), primarily nausea, miscellaneous disturbances (1 1%), primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary

Incidence in Controlled Clinical Trials—Adverse events reported by 1% or more of 477 patients who received buspirone in four-week, controlled trials. *Cardiovascular:* Tachycardia/palpitations 1% *CNS:* Dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, lightheadedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2%. *EENT* Blurred vision 2% *Gastrointestinal* Nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1% *Musculoskeletal* Musculoskeletal aches/pains 1% *Neurological* Numbness 2%, paresthesia 1%, incoordination 1%, tremor 1% *Skin* Skin rash 1% *Miscellaneous:* Headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%

Other Events Observed During the Entire Premarketing Evaluation—The relative frequency of all other undesirable events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under well-controlled, open, and uncontrolled conditions is defined as follows: Frequent are those occurring in at least 1/100 patients, infrequent are those occurring in 1/100 to 1/1000 patients, and rare are those occurring in less than 1/1000 patients. *Cardiovascular*—frequent: nonspecific chest pain; infrequent: syncope, hypotension, hypertension, rare: cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, bradycardia. *Central Nervous System*—frequent: dream disturbances, infrequent: depersonalization, dysphoria, noise intolerance, euphoria, akathisia, tearfulness, loss of interest, dissociative reaction, hallucinations, suicidal ideation, seizures; rare: feelings of claustrophobia, cold intolerance, stupor, slurred speech, psychosis *EENT*—frequent: tinnitus, sore throat, nasal congestion, infrequent: redness and itching of the eyes, altered taste, altered smell, conjunctivitis; rare: inner ear abnormality, eye pain, photophobia, pressure on eyes *Endocrine*—rare: galactorrhea, thyroid abnormality *Gastrointestinal*—infrequent: flatulence, anorexia, increased appetite, salivation, irritable colon, rectal bleeding, rare: burning of the tongue. *Genitourinary*—infrequent: urinary frequency, urinary hesitancy, menstrual irregularity and spotting, dysuria; rare: amenorrhea, pelvic inflammatory disease, enuresis, nocturia. *Musculoskeletal*—infrequent: muscle cramps, muscle spasms, rigid/stiff muscles, arthralgias. *Neurological*—infrequent: involuntary movements, slowed reaction time; rare: muscle weakness *Respiratory*—infrequent hyperventilation, shortness of breath, chest congestion; rare: epistaxis *Sexual Function*—infrequent: decreased or increased libido; rare: delayed ejaculation, impotence. *Skin*—infrequent: edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema, blisters; rare: acne, thinning of nails *Clinical Laboratory*—infrequent: increases in hepatic aminotransferases (SGOT, SGPT), rare: eosinophilia, leukopenia, thrombocytopenia *Miscellaneous*—infrequent: weight gain, fever, roaring sensation in the head, weight loss, malaise, rare: alcohol abuse, bleeding disturbance, loss of voice, hiccoughs.

Postintroduction Clinical Experience—Rare occurrences of allergic reactions, cogwheel rigidity, dystonic reactions, ecchymosis, emotional lability, tunnel vision, and urinary retention have been reported Because of the uncontrolled nature of these spontaneous reports, a causal relationship to BuSpar has not been determined

Drug Abuse and Dependence: ***Controlled Substance Class***—Not a controlled substance

Physical and Psychological Dependence—Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence However, since it is difficult to predict from experiments the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (eg, development of tolerance, incrementation of dose, drug-seeking behavior).

Overdosage: ***Signs and Symptoms***—At doses approaching 375 mg/day the following symptoms were observed nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. No deaths have been reported in humans either with deliberate or accidental overdosage.

Recommended Overdose Treatment—General symptomatic and supportive measures should be used along with immediate gastric lavage No specific antidote is known and dialyzability of buspirone has not been determined

For complete details, see Prescribing Information or consult your Mead Johnson Pharmaceuticals Representative.

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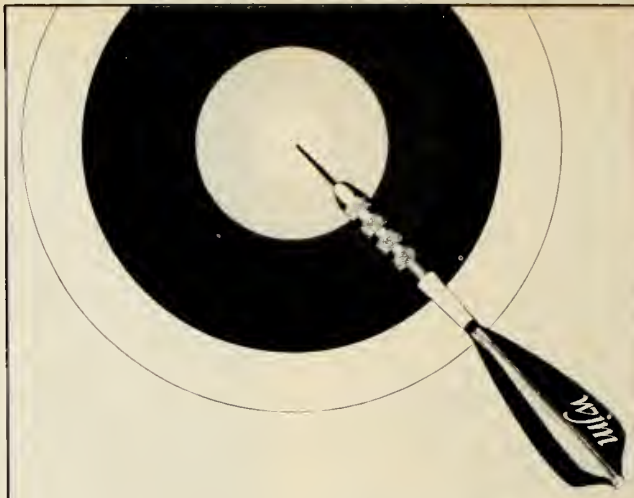

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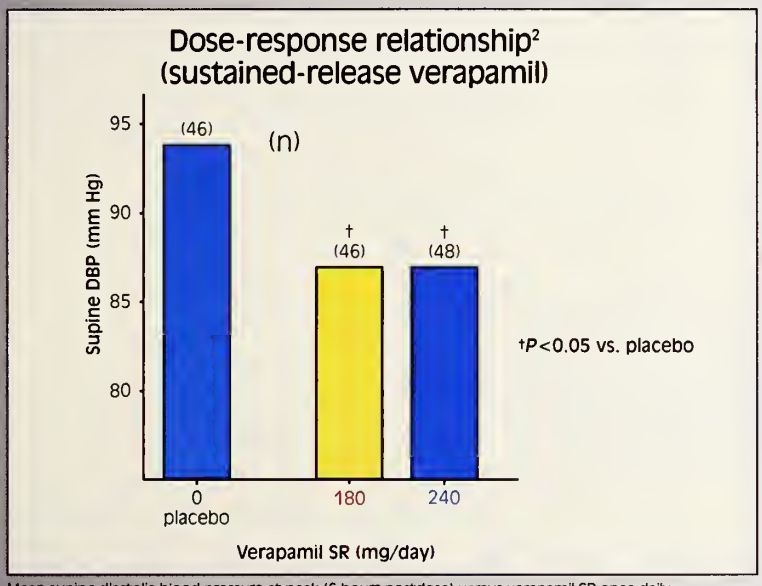

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BRIEF SUMMARY

Contraindications: Severe LV dysfunction (see *Warnings*), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), hypersensitivity to verapamil.

Warnings: Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol clearance may occur with combined use. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractilit AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients wi hypertrophic cardiomyopathy should be avoided, since significant hypotension may resu Concomitant use of lithium and verapamil may result in a lowering of serum lithium levels increased sensitivity to lithium. Patients receiving both drugs must be monitored careful Verapamil may increase carbamazepine concentrations during combined use. Rifampin may redu verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increa serum levels of cyclosporin. Concomitant use of inhalation anesthetics and calcium antagonis needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentia the activity of neuromuscular blocking agents (curare-like and depolanzing); dosage reducti may be required. Adequate animal carcinogenicity studies have not been performed. One stu in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Am test. Pregnancy Category C. There are no adequate and well-controlled studies in pregna women. This drug should be used during pregnancy, labor, and delivery only if clearly neede Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapa use.

Adverse Reactions: Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5 headache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4 bradycardia: HR < 50/min (1.4%), AV block: total 1°,2°,3° (1.2%), 2° and 3° (0.8%), ra (1.2%), flushing (0.6%), elevated liver enzymes. The following reactions, reported in 1.0% less of patients, occurred under conditions where a causal relationship is uncertain: ang pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitatio purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplas ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomn muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, arthralgia and ra exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndro erythema multiforme, blurred vision, gynecomastia, increased urination, spotty menstruati impotence.

References:

1. 1988 Joint National Committee: The 1988 report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med* 1988;148:1023-1038.
2. Data on file, G.D. Searle & Co.

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Discussant: THOMAS N. DEWAR, MD

A discussion selected from the weekly staff conference in the Department of Medicine, University of California, San Francisco. Taken from a transcription, it was edited by Homer A. Boushey, MD, Professor of Medicine, and Nathan M. Bass, MD, PhD, Associate Professor of Medicine, under the direction of Lloyd H. Smith, Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine.

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PIERO MUSTACCHI, MD

From the Department of Epidemiology and Biostatistics and the Department of Medicine, University of California, San Francisco, School of Medicine.

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Dr Combs is Professor of Nutrition, Division of Nutritional Sciences, Cornell University, Ithaca, New York.

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Dr Brater is Professor of Medicine and Pharmacology and Director of Clinical Pharmacology, Indiana University School of Medicine, Indianapolis.

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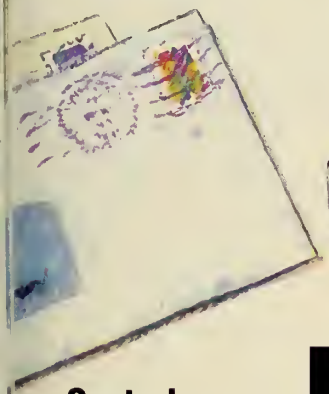

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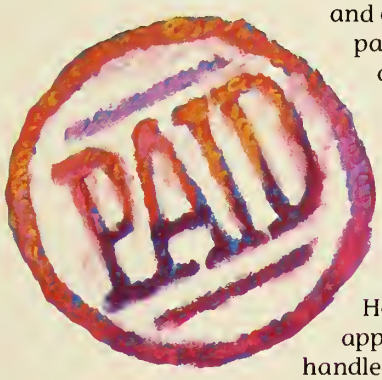

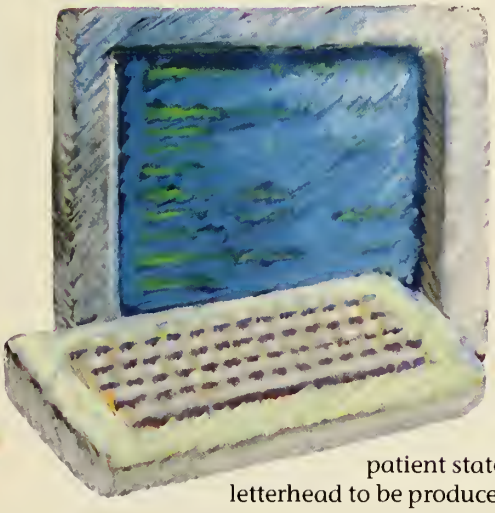

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Brochures and registration forms are available from the contact person or organization sponsoring the program.

September 7-9—**Geriatrics of the '90s: Clinical Management of the Elderly Patient.** Symposia Medicus at The Princess Resort, Scottsdale. Fri-Sun. Contact: Jim Goodrich, (415) 935-7889.

September 8-9—**Pulmonary and Infectious Diseases.** Mayo Clinic-Scottsdale at Los Abrigados Resort, Sedona. Sat-Sun. Contact: Jodi Lee Smith, (602) 391-8300.

October 5-6—**Cancer Reviews.** Mayo Clinic-Scottsdale at Orange Tree Golf and Conference Center, Scottsdale. Fri-Sat. Contact: Jodi Lee Smith, (602) 391-8300.

October 19-20—**Common Clinical Problems in the Elderly and Nursing Home Care.** Arizona Geriatrics Society at Arizona Golf Resort and Conference Center, Mesa. Fri-Sat. Contact: Marian Richardson, (602) 974-4212.

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This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 541-0900. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ALLERGY

September 15—**Diagnostic and Therapeutic Choices in Allergy and Immunology.** Los Angeles Society of Allergy and Clinical Immunology at Regent Beverly Wilshire Hotel, Beverly Hills. Sat. 8 hrs. Contact: Sherri Cartwright, 1626 N Wilcox, No 557, Hollywood 90028. (818) 240-6735.

September 22—**Allergy and the Environment.** Allergy Foundation of Northern California at Portman Hotel, San Francisco. Sat. 7 hrs. Contact: Theodore Chu, MD, (408) 243-2700.

ANESTHESIOLOGY

September 8-9—**Case Conference in Anesthesia.** California Society of Anesthesiologists at Lake Tahoe, California. Sat-Sun. 20 hrs. $175. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

October 28-November 2—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Westin Maui Hotel, Kaanapali Beach, Hawaii. Sun-Fri. 20 hrs. $345. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

January 20-26—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Sheraton Hotel, Poipu Beach, Kauai. Sun-Sat. 20 hrs. $345. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

November 16-18—**Anesthesiology Update: 1990.** UCD at Monterey Plaza. Fri-Sun. Contact: UCD.

CARDIOLOGY

August 17-18—**Series IV—Cardiac Wellness and Rehabilitation.** Medical Education Resources at Doubletree Inn, Monterey. Fri-Sat. 11 hrs. $295. Contact: MER, 1500 W Canal Court, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

September 14-15—**Series I—Coronary Heart Disease Update.** Medical Education Resources at Las Vegas Hilton. Fri-Sat. 11 hrs. $295. Contact: MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80123. (800) 421-3756.

October 13—**Myocardial Infarction: Contemporary Management.** UCD at Hyatt Regency, Sacramento. Sat. Contact: UCD.

KEY TO ABBREVIATIONS

CMA: California Medical Association
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DREW: Charles R. Drew Postgraduate Medical School
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LLU: Loma Linda University
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UCD: University of California, Davis
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UCI: University of California, Irvine
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UCLA: University of California, Los Angeles
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UCSD: University of California, San Diego
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UCSF: University of California, San Francisco
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USC: University of Southern California
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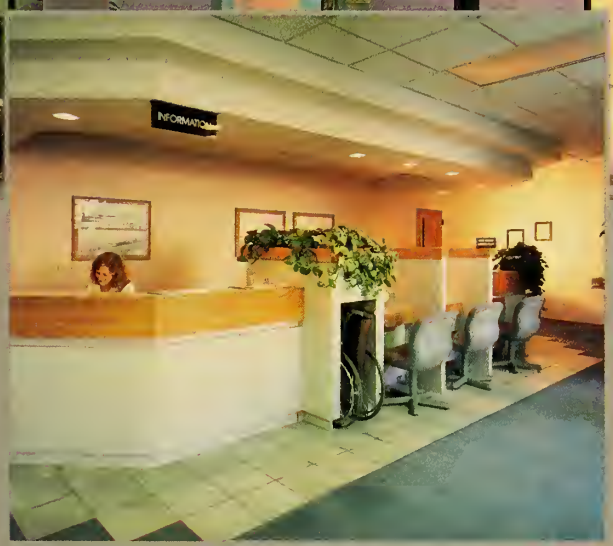

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The Western Journal of Medicine

(ISSN 0093-0415/USPS 084 480) is published monthly for $35 per year (USA and Canada) by the California Medical Association, 221 Main Street, San Francisco, CA 94105. Second-class postage paid at San Francisco and additional mailing offices.

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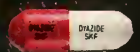

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If hypokalemia is suspected, obtain an ECG and monitor serum potassium. If hypokalemia develops, discontinue 'Dyazide' and initiate thiazide therapy if needed. Persistent hypokalemia may require dialysis. Monitor serum electrolytes frequently in patients with mild renal dysfunction and in diabetic patients. In patients who may develop respiratory or metabolic acidosis, monitor serum electrolytes and acid/base balance frequently.

Precautions: *The bioavailability of the hydrochlorothiazide and triamterene components of 'Dyazide' is about 50% of the maximum obtainable with oral therapy. Theoretically, a patient transferred from therapy with hydrochlorothiazide with or without triamterene might show an increase in blood pressure, fluid retention, or change in serum potassium. Extensive clinical experience with 'Dyazide', however, suggests that these conditions have not been commonly observed in clinical practice. (See CLINICAL PHARMACOLOGY.) Use thiazides cautiously in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease; potassium depletion induced by the thiazide may be important in this connection; administer 'Dyazide' cautiously and be alert for such early signs of impending coma as confusion, drowsiness and tremor; if mental confusion increases, discontinue 'Dyazide' for a few days; attention must be given to other factors that may precipitate hepatic coma, such as blood in the gastrointestinal tract or preexisting potassium depletion. If patients develop hypokalemia, which is uncommon with 'Dyazide', increase potassium intake (i.e., with supplements or potassium-rich foods). If repeat determinations show serum potassium concentrations below 3.0 mEq/L, discontinue 'Dyazide' and initiate potassium chloride supplementation. Institute corrective measures cautiously and monitor serum potassium concentrations frequently, especially in patients receiving digitalis or those with a history of cardiac arrhythmias. Diuretics may aggravate existing electrolyte imbalances, especially at high dosages or in patients on salt-restricted diets. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Chloride replacement may be required in the treatment of metabolic acidosis. If dilutional hyponatremia develops, restrict water intake, to actual salt depletion, initiate sodium chloride replacement. Use 'Dyazide' cautiously in patients with a history of renal stone formation.*

If hyperkalemia develops when treating for hypokalemia, take corrective measures. Also discontinue 'Dyazide' and, if appropriate, substitute a thiazide diuretic until potassium levels return to normal. Do periodic BUN and serum creatinine determinations, especially in the elderly and in patients with suspected or confirmed renal insufficiency. Serum PBI levels may decrease without signs of thyroid disturbance. Discontinue thiazides before conducting parathyroid function tests.

Angiotensin-converting enzyme (ACE) inhibitors can elevate serum potassium; use with caution with 'Dyazide'. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine; therefore use cautiously in patients undergoing surgery. Monitor electrolytes in patients taking amphotericin B, corticosteroids or corticotropin concomitantly. Thiazides may potentiate the action of other antihypertensive drugs. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be needed. 'Dyazide' may raise the level of blood uric acid; dosage adjustments of antigout medication may be needed to control hyperuricemia and gout. The following agents given with triamterene may promote serum potassium accumulation and possibly result in hyperkalemia, especially in patients with renal insufficiency: blood from blood bank (may contain up to 30 mEq of potassium per liter of plasma or up to 65 mEq of potassium per liter of whole blood when stored for more than 10 days); low-salt milk (may contain up to 60 mEq of potassium per liter); potassium-containing medications (such as parenteral penicillin G potassium), and salt substitutes (may contain substantial amounts of potassium). Exchange resins, such as sodium polystyrene sulfonate, whether administered orally or rectally, reduce serum potassium concentrations by sodium replacement of the potassium; fluid retention may occur in some patients because of the increased sodium intake. Chronic or overuse of laxatives may reduce serum potassium concentrations by promoting excessive potassium loss from the gastrointestinal tract; laxatives may interfere with the potassium-retaining effects of triamterene. The effectiveness of methenamine may be decreased when used concurrently with hydrochlorothiazide because of alkalinization of the urine. 'Dyazide' will interfere with the fluorescent measurement of quinidine.

There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy only if clearly needed. Thiazides and triamterene cross the placental barrier and appear in cord blood. The use of thiazides in pregnancy requires weighing the anticipated benefit against possible hazards, including fetal or neonatal jaundice, pancreatitis, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. Thiazides appear, and triamterene may appear, in breast milk. If use of the drug is essential, the patient should stop nursing. Safety and effectiveness in children have not been established.

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Biomedical Science

Compliance and Outcome in Anorexia Nervosa

HANS STEINER, MD; CLIFF MAZER, LCSW; *and* IRIS F. LITT, MD, *Stanford, California*

Anorexia nervosa is notoriously difficult to treat, but little is known regarding the relationship of compliance to treatment outcome. We investigated in 41 adolescents who fulfilled DSM-III-R criteria for anorexia nervosa, the relationship between the completion of a standard psychosocial treatment program, subtypes of anorexia nervosa, and outcome as determined by standardized measurements. These adolescents were observed for an average of 32.4 months. Overall, 29 patients (70%) improved considerably, but 10 (24%) were symptomatic, and 2 (5%) remained in poor condition. There were no deaths. Of the 41 patients, 14 (34%) completed our entire treatment program, 15 (37%) received major treatment and failed in the outpatient follow-up phase only, 7 (17%) dropped out of inpatient treatment before its completion, and 5 (12%) refused treatment in our system altogether. Of all the dropouts, 10 received no further treatment. One patient was admitted to hospital elsewhere but again dropped out in the outpatient phase of that program. Seven patients (17%) received further outpatient treatment only, and 9 (22%) received inpatient and outpatient care and seemingly completed their treatment. Treatment completion significantly affected the measures of global clinical functioning and specific psychopathologic features, but only for those patients who completed the initial program. Bulimic patients did considerably worse on follow-up and were less likely to complete treatment. Patients with restricted anorexia nervosa were more likely to complete treatment than those with a bulimic subtype ($P = .03$). Differential compliance rates in the two subtypes confound the effects of treatment completion and need to be controlled for in future studies. Depression was not associated with noncompliance but, if present, was associated with poor outcome on follow-up and abated in only a third of those in whom it was initially present.

(Steiner H, Mazer C, Litt IF: Compliance and outcome in anorexia nervosa. West J Med 1990 Aug; 153:133-139)

Although the literature is replete with descriptions of the difficulties of working with patients with anorexia nervosa, especially of engaging them in treatment, few studies systematically address the role of compliance in the treatment outcome. Only one study to date has related compliance to outcome in the treatment of anorexia nervosa. Vandereycken and Pierloot retrospectively studied 133 female patients admitted to hospital because of anorexia nervosa and found a remarkably high dropout rate of 50% during the first year.[1] Educational and social statuses were significantly lower in the dropouts. Patients with exposure to behavior modification had a higher dropout rate than those who had their caloric intake prescribed by their physicians. On follow-up, there was no difference in mortality between groups. Body weight on follow-up was considerably lower in the dropout group. The authors detected only two patients who had improved without further treatment. No detailed information about the patients' psychopathology was available. Isager and co-workers, reporting on death and survival rates in 151 consecutive patients with anorexia nervosa, found that relapse rates were twice as high if patients were seen for less than a year, and patients in therapy for longer than that had a considerably smaller chance for relapse.[2] Russell and colleagues reported an evaluation of family therapy for eating disorders,[3] with the following distribution of treatment completion: 9% refused treatment altogether after treatment in the hospital; 10% dropped out within three months; 16% dropped out sometime after three months. Thus, 35% did not complete outpatient treatment. No information was given regarding the patients' inpatient program completion rate. There was a greater tendency for bulimic than anorexic patients to drop out. Dropping out affected outcome; dropouts were notably worse off at the one-year prospective follow-up on a variety of outcome measures. No information was available on whether dropouts received treatment elsewhere and how it might have affected their condition. Other studies addressed compliance,[4-8] but only a few were systematic[5] and only some provided unsystematic follow-up.[6-8]

The phenomenon of the treatment dropout is by no means unique to the treatment of anorexia nervosa.[9] Most studies of treatment outcome fail to include the entire inception cohort, thereby allowing for the overrepresentation of those with successful outcomes. According to Sackett and Haynes,

> [T]he systematic loss to analysis of the most noncompliant patients (those who drop out entirely or who rarely attend appointments) invalidates the conclusions of a large number of compliance investigations and this failure cannot be overcome by statistical or pharmacologic maneuvers.[10(p22)]

In other psychiatric conditions, individual psychotherapy dropout rates are related to socioeconomic status, educational level,[9,11] and, possibly, sex, age, patient and therapist factors, and sociodemographic factors. Szmukler and associates found that bulimic symptoms, expressed emotion by parents, and the type of therapy offered all interacted to cause dropouts.[6]

Although the general quality of outcome studies of anorexia nervosa has improved substantially over the past five to ten years,[12-25] it is unclear how many studies report on the entire inception cohort. Patients dropping out of treat-

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ABBREVIATIONS USED IN TEXT

DSM-III-R = *Diagnostic and Statistical Manual of Mental Disorders,* third edition, revised
EAT = Eating Attitude Test
EDI = Eating Disorders Inventory
GCS = Garfinkel global clinical score
MANOVA = multivariate analysis of variance

ment often are not included in the final analysis, thus artificially inflating treatment effect and obscuring differential effects of different treatments. In a recent review, Agras and Kraemer concluded that there is little evidence that different treatments have different outcomes.[24] A lack of accounting for differential compliance rates in different treatment conditions might well contribute to this finding.

Two other factors could be related to the lack of evidence for differential treatment effects: Several subcategories of anorexia nervosa influence the course of illness, such as the presence or absence of depression and the presence of bulimic symptoms.[12,17,23] The distribution of these subtypes should be controlled for to prevent uneven loading of various treatment methods. In addition, outcome is too narrowly defined in terms of weight and return of menses only—relatively convenient measures. More recently, sophisticated methods have become available to measure the more refined psychopathologic features of the syndrome. These permit an assessment of functional areas that might be influenced by treatment independent of weight and menstrual state.

We hypothesized that patients completing treatment would have more substantial reductions in specific eating disorders and behavior, along with larger reductions in depressive and bulimic symptoms. We also hypothesized that persistent bulimic symptoms and depression would be associated with a poor prognosis. At the Eating Disorders Program at Children's Hospital, Stanford (California) Medical Center, we were able to explore these factors in greater detail. Our first 50 patients were treated by psychosocial interventions only within a standard treatment program. Thus, we could test hypotheses regarding the effects of compliance on the outcome of anorexia nervosa.

Patients and Methods

Patients

We invited our first 50 patients to participate in the study; 41 (82%) gave informed consent. These 41 patients were evaluated by individual and family interviews. The follow-up sample, as well as the nine patients who refused to provide follow-up information, was not significantly different from our total population of eating disorder patients on various psychopathologic or demographic variables. Of the nine patients who refused to participate in the study, three had none or minor treatment, four had major treatment, and two completed treatment in our program. Reasons for not participating in the study were varied, but one of the most often cited was that the patient and the family did not want to be reminded of the illness. All subjects satisfied minimum criteria for inclusion in the study, which included a primary diagnosis of anorexia nervosa based on criteria of the *Diagnostic and Statistical Manual of Mental Disorders,* third edition, revised (DSM-III-R), by two of us (H.S. and I.F.L.), and at least a year had elapsed since the initial hospital treatment and discharge. In addition, both authors assigned patients to either "restrictive" or "bulimic" subgroups. Restrictive anorexia nervosa was diagnosed when patients achieved weight loss by dieting and increased caloric expenditure alone. Patients were assigned to the bulimic subgroup when frequent (at least once a week for a month) overeating or purging was present. Accordingly, in the sample 30 (73%) patients had restrictive and 11 (27%) bulimic features. The mean age at diagnosis was 14.8 ± 2.4 years, and the mean age at the start of illness was 13.0 ± 2.0 years ($\pm$ the standard deviation). The mean duration of illness before diagnosis was 9.8 ± 8.4 months, the mean age at follow-up was 17.6 ± 2.2 years, and the actual length of the follow-up period ranged between 12 and 72 months with a mean of 32.4 months. The male-to-female ratio was 1:6.

Follow-up Interviews

All follow-up interviews were carried out by one of us (C.M.), who was not present in the program when these patients were treated. All patients completed a follow-up diagnostic battery and a standardized interview modeled after a University of California, Los Angeles, follow-up study.[27] The DSM-III-R criteria for diagnosis were applied for the diagnosis of both anorexia nervosa and a secondary diagnosis of depression.

Measurements

The following measures were obtained from all subjects at baseline—that is, in the two-week diagnostic period preceding intervention—the Zung Self-Rating Depression Scale, which is a reliable and valid self-report inventory of depressive symptoms[28]; the Eating Attitude Test-26 (EAT), a 26-item, self-report questionnaire designed to measure objectively the presence of disturbed eating patterns and the symptoms of anorexia nervosa (the Eating Attitude Test has an α-reliability coefficient of 0.90)[29]; the Garfinkel global clinical score (GCS) for the assessment of anorexia nervosa.[22] The last measures body weight, menstrual state, eating habits, and social and vocational adjustment. Scores between 0 and 4 are considered asymptomatic and between 5 and 8 mildly, 9 and 13 moderately, and 13 and above severely symptomatic. The average score in our clinic population is 11.5 ± 4.5. These ratings were given by two independent raters between whom reliability was 0.82.

All these measures were repeated at follow-up. We also added the Eating Disorders Inventory (EDI),[30] which had then just become available. This is a 64-item, 8-factor, self-report questionnaire measuring specific features of eating disorders. The eight factors are a drive for thinness, bulimia, body dissatisfaction, ineffectiveness, interpersonal distrust, perfectionism, interoceptive awareness, and maturity fears.

Treatment Program

Our program has been described in detail elsewhere.[31] Briefly, it consists of an average treatment period of 16 months. Following a two-week diagnostic outpatient phase, a mean of six weeks is spent as an inpatient. Follow-up psychotherapy after the hospital stay extends for an average of 30 family sessions and 63 individual sessions. While in the hospital, patients receive behavior modification for weight gain, nutritional counseling, a medical evaluation, daily supportive group psychotherapy, and individual and family psychotherapy. Individual psychotherapy incorporates the principles stated by Bruch[32] and consists of three to five sessions per week as inpatients and weekly sessions as outpatients. Family therapy proceeds according to principles outlined by Minuchin and co-workers[33] and consists of biweekly inpatient or weekly or fewer outpatient sessions. All psychotherapeutic procedures were supervised by

one of us (H.S.). Three fourths of the family therapy was actually carried out by this author (H.S.), the rest by child psychiatry fellows under supervision. Group therapy occurred daily during the hospital stay and was supportive in nature. Behavior modification was offered on a fixed, internal, one-day reinforcement schedule during inpatient stays[23] for an average of about six weeks and produced a mean 5.2-kg weight gain. Daily nutritional counseling was available for inpatients and weekly counseling for outpatients. Vital signs and physiologic variables were monitored and feedback given daily during the hospital admission and weekly or biweekly on an outpatient basis by the staff of the Division of Adolescent Medicine (supervised by one of us [I.F.L.]). All treatment components were coordinated weekly in a therapeutic team meeting with patients' participation.

On the basis of the extent of their participation in the program at termination, patients were assigned therapy scores as follows:

0 = Treatment refusal: These patients were in our treatment program less than a week, permitting only diagnostic assessment;

1 = Partial treatment: These patients remained longer than a week but less than six weeks (mean duration of inpatient treatment in our program);

2 = Major treatment: These patients remained more than six weeks in our program, usually completing the inpatient portion of their treatment, but not completing their course of outpatient follow-up against the recommendations of the treatment team. Patients were medically and psychiatrically symptomatic when they decided to stop outpatient therapy;

3 = Complete treatment: These patients completed the diagnostic inpatient and outpatient phase and terminated with the consent of the treatment team. These patients were usually considered by the treatment team both medically and psychiatrically asymptomatic and stable.

Statistics

We applied a multivariate analysis of variance (MANOVA) with Roy's greatest root to test for differences on all outcome variables between groups, with a one-way median analysis as a follow-up procedure. Furthermore, Pearson's product moment correlation, Student's *t* test, and χ^2 with Yates's correction were employed as appropriate.

Results

Outcome in Total Sample

In general, the outcome was relatively good. Of the 41 patients, 15 (37%) were in the asymptomatic range (GCS 0 to 3), 14 (34%) in the symptomatic but improved range, 10 (24%) in the very symptomatic range (GCS 8 to 11), and 2 (5%) in the poor category (GCS 12 or worse). There were no deaths. The whole sample showed improvement from diagnosis on the global clinical score (12.3 ± 3.5 versus 5.3 ± 3.3, $t = 9.8$, $P < .001$), ideal body weight percentage ($80\% \pm 10\%$ versus $93\% \pm 12\%$, $t = 4.9$, $P < .001$), and Eating Attitude Test scores (53 ± 15 versus 24 ± 18, $t = 7.9$, $P < .001$), all by the two-tailed *t* test.

The total EAT and EDI scores and all EDI subscales except "maturity fears" and "perfectionism" showed a significant correlation with the global clinical score on follow-up, ranging from $+0.646$ to 0.378 ($P < .05$). These correlations indicate that those patients who appeared symptomatic to our rater also showed a persistent specific eating disorder by self-report, thus cross-validating our ratings.

At follow-up, of the 35 female patients, 16 (46%) had persistent amenorrhea, 7 (20%) had irregular menses, and 12 (34%) were menstruating monthly. Vomiting occurred in 9 of the 41 patients (22%) on diagnosis and at follow-up. Bingeing occurred in 14 (34%) at follow-up, a slight increase over the 10 (24%) at time of diagnosis. Laxatives were abused by 4 (10%) on follow-up, essentially unchanged from diagnosis (3 [7%]).

In terms of social adjustment, 10 (24%) patients were rated as not having any problems, 20 (49%) as having mild, 8 (20%) as having moderate, and 3 (7%) as having severe problems. Educational and vocational problems were absent in 26 (63%), mild in 9 (22%), moderate in 4 (10%), and severe in 2 (5%) patients.

The rate of readmission to a hospital was 29% (12 of 41 patients). Five patients were readmitted once, three were readmitted twice, and four were readmitted three times. In this category, there was a significant difference between patients with bulimic features and those with restrictive anorexia. Of 11 patients with bulimia, 7 (64%) had to be readmitted, but only 5 of 25 with restrictive anorexia (20%) were readmitted (χ^2 4.26, degree of freedom [*df*] 1, $P < .05$). The presence or absence of depression did not relate to the readmission rate.

Compliance With Treatment

Treatment score 0 (n = 5). Five patients (12%) refused any treatment. Of these, two did and three did not receive any further treatment outside our system. At follow-up, one was improved in that she had no further problems with weight or bingeing and purging and she had a return of her menses. The second patient was improved in terms of weight, but binged-purged uncontrollably. The third was highly symptomatic both in terms of weight and binge-purge pathology (GCS 13); this was unchanged from diagnosis. The other two refusing treatment had either inpatient (one patient) or only outpatient follow-up (one patient). On follow-up, both these patients had improved, but both were in the symptomatic range (GCS 5 to 8). Spontaneous recovery seems to have occurred in only one patient in this group; her initial global clinical score was 16.

Treatment score 1 (n = 7). Of the seven patients (17%) who had received only minimal intervention in our program—inpatient treatment dropouts—only one did not have any further treatment at all. He had improved substantially, although a three-week hospital stay in our program produced only a modest weight gain (2 kg). His global clinical score was 12 on diagnosis and 0 on follow-up. All other patients in this category had either inpatient and outpatient treatment (four) or outpatient-only treatment (two) in other systems.

Treatment score 2 (n = 15). Of these 15 patients, 6 (14%) had no further treatment, 5 were admitted to hospital and had outpatient treatment elsewhere, and 4 had only outpatient treatment in another program. Of the six with no further treatment in this group, four were in the symptomatic but improved category; one patient remained in the poor category. One patient was asymptomatic (GCS 3).

Treatment score 3 (n = 14). None of the 14 patients (34%) in the completed-treatment group required any additional treatment by the time of the 32-month follow-up. Nine were in the asymptomatic range, four had improved but were symptomatic, and only one was in the very symptomatic group because of the emergence of binge-purging in a patient with previous restrictive anorexia. Thirteen patients with restrictive anorexia and one with bulimic fea-

tures completed the program. Depression as a secondary diagnosis did not predict initial treatment completion.

Summary of Post-Dropout Treatment in Other Settings

Of the 27 patients who dropped out at any stage of treatment in our program, 17 received further treatment elsewhere. Of those 17 patients, 9 (22%) received both inpatient and outpatient care and seemed to complete their treatments, 1 was treated as an inpatient only, and 7 (17%) were treated as outpatients only. Patients who did not seek treatment after dropout were distinguished by the presence and degree of depression. Patients who continued in treatment were more likely to have a secondary diagnosis of major depression (7 of 10 versus 4 of 17; $\chi^2 = 3.87$, *df* 1, $P = .05$) and had higher Zung scores on diagnosis (51.5 ± 15 versus 41.5 ± 15, $t = 1.66$, $P = .05$ one-tailed). These groups did not differ on any other variable. Specifically, bulimic and restrictive features did not predict treatment status after the initial dropout.

Analysis of the Effects of Initial Treatment Completion

For the purposes of this analysis, we combined treatment refusers (score 0) and patients with only minimal treatment into one group (n = 12), contrasting this group with those patients who had received major (score 2, n = 15) and complete (score 3, n = 14) treatment. There were no significant differences among these groups at diagnosis on the basis of age, sex, socioeconomic status, duration of illness, global clinical score, Zung and EAT scores, previous treatment, or duration of follow-up, indicating that these groups were comparable in terms of important measures of chronicity and psychopathology. Table 1 summarizes the findings on follow-up.

TABLE 1.—*Outcome in Treatment Groups of Anorexia Nervosa in 41 Adolescent Patients*

	*Treatment Group**†			
Outcome Variable	*Incomplete, n = 12*	*Major, n = 15*	*Complete, n = 14*	*Significance*
GCS				
At diagnosis	11.8 ± 2.9	12.1 ± 2.8	11.4 ± 2.7	NS
At follow-up	6.7 ± 3.5	5.7 ± 3.4	3.6 ± 2.1	‡
Ideal body weight %				
At diagnosis	85 ± 14	78 ± 12	74 ± 2.7	NS
At follow-up	92 ± 8	89 ± 9.6	94 ± 9	NS
Menses, Reg/Irreg/None				
At diagnosis	0/2/7	1/0/12	1/0/13	NS
At follow-up	3/2/4	4/1/8	5/3/6	NS
GCS, social adjustment				
At diagnosis	3.6 ± 1.1	4.1 ± 1.5	3.6 ± 1.8	NS
At follow-up	2.7 ± 2.1	1.7 ± 1.4	0.9 ± 0.5	§
Zung				
At diagnosis	47 ± 16	44 ± 16	40 ± 13	NS
At follow-up	41 ± 8	39 ± 15	37 ± 8	NS
EAT				
At diagnosis	48 ± 15	46 ± 14	47 ± 18	NS
At follow-up	25 ± 16	28 ± 12	18.3 ± 18.1	¶
EDI				
At follow-up	45 ± 30	53 ± 31	28 ± 29	‖

Irreg = irregular, NS = not significant, Reg = regular

*Explanation of treatment groupings: Incomplete = treatment scores 0 and 1, Major = treatment score 2, Complete = treatment score 3. See text for a thorough discussion of treatment differences. Higher scores on the global clinical score (GCS), Eating Attitude Test (EAT), Eating Disorders Inventory (EDI), and the Zung Self-Rating Depression Scale indicate more severe disease.

†Except for Menses, scores are given as the mean ± standard deviation.

‡Median one-way analysis: $\chi^2 = 7.2$, $df = 2$, $P = .03$.

§Median one-way analysis: $\chi^2 = 10.0$, $df = 2$, $P = .006$.

¶Median one-way analysis: $\chi^2 = 4.66$, $df = 2$, $P = .09$.

‖Median one-way analysis: $\chi^2 = 6.53$, $df = 2$, $P = .04$.

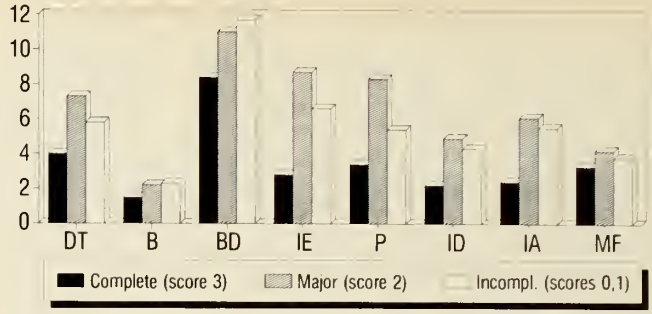

Figure 1.—The graph shows the Eating Disorder Inventory results in anorexic patients at follow-up by subscale (multivariate ANOVA, Roy's greatest root = 0.661, F[8,32] = 2.64, $P = .02$). DT = drive for thinness, B = bulimia, BD = body dissatisfaction, IE = ineffectiveness, P = perfectionism, ID = interpersonal distrust, IA = interoceptive awareness, MF = maturity fears

By MANOVA, there were significant overall differences among treatment groups on the continuous outcome variables, GCS, EDI, EAT, Zung (Roy's greatest root = 0.338, F [4,36] = 3.04, $P = .03$). One-way median analyses at follow-up showed substantially lower GCS, EAT, and EDI scores in those completing treatment. The differences in GCS remained significant when the ratings of social adjustment are looked at alone, omitting eating habits, body weight, and menstrual status. Zung scores, however, did not differentiate the groups and neither did ideal body weight percentage and menstrual status.

When MANOVA was applied to the subscales of the EDI (Figure 1), significant differences were found (Roy's greatest root = 0.661, F[8,32] = 2.64, $P = .02$). Patients completing treatment scored notably lower on drive for thinness, body dissatisfaction, ineffectiveness, perfectionism, interpersonal distrust, and lack of interoceptive awareness.

Effects of Treatment in Other Settings

In the course of the follow-up interviews, we also obtained information regarding what kind of treatment the patients had received and grouped them as follows:

- none (10 patients);
- partial (8 patients). Patients received either inpatient or outpatient treatment, but, as best we could tell, they did not complete these programs either;
- major (9 patients). These patients usually received both inpatient and outpatient intervention and seemed to follow through to termination.

These groups did not differ at diagnosis with regard to restrictive or bulimic features, GCS or EAT scores, age, sex, or socieconomic status. They did differ in terms of the secondary diagnosis of depression; none of the ten patients who had gone on without further intervention had such a diagnosis, but four of the eight with partial treatment and six of those with major treatment did ($\chi^2 = 9.85$, *df* 2, $P = .007$).

The MANOVA on the outcome variables of these subgroups was significant (Roy's greatest root = 0.853, F (4,21) = 4.5, $P = .009$) (Table 2). One-way median analyses showed the significant differences on Zung scores and on the ratings of the social-vocational functioning of the GCS (Table 2). There were no significant differences on EDI, EAT, and GCS scores or weight or menses at follow-up.

When all three groups are compared with those who completed treatment in our program, patients completing treatment are found to consistently achieve the lowest scores of all groups on the GCS, the social-adjustment portion of the GCS, the EDI and EAT, and the second lowest

score (after those with no follow-up treatment at all) on the Zung (compare Table 1). Some of the differences were significant by one-way median analysis—GCS: $\chi^2 = 8.61$, df 3, $P = .01$; GCS, social-vocational adjustment: $\chi^2 = 8.25$, df 3, $P = .02$; EAT: $\chi^2 = 6.2$, df 3, $P = .05$; EDI: $\chi^2 = 8.04$, df 3, $P = .02$. Ideal body weight percentage, menses, and Zung scores were not significantly different.

Outcome of Patients With Anorexia With Bulimic Features

On admission, patients with anorexia with bulimic features did not differ from those with restrictive features in terms of sex, socioeconomic status, age, duration of illness, length of hospital stay, duration of follow-up, and previous interventions. They did differ on the global clinical severity score ($t = 4.69$, $P < .001$), reflecting the rating system's added severity points for binge-purge behavior. They also differed on admission weight ($t = 2.93$, $P < .01$), with anorexic patients with bulimia being closer to their ideal body weight (87% ± 15%) than those with restrictive anorexia (72% ± 13%). On follow-up, bulimic anorexic patients were considerably worse off on six of nine measures than were those with restrictive anorexia (Table 3). Depression scores and outcome for weight and menses were not significantly different, but these patients had greater difficulty on follow-up with specific eating disorder psychopathology as measured by the Eating Disorders Inventory. These differences remained significant when bulimic behavior was corrected for by subtracting the bulimia subscale from the total.

Their elevated global clinical scores originate not only from binge-purge behavior but from their social adjustment in general. As previously indicated, fewer anorexic patients with bulimic features than with the restrictive type completed our treatment program, reflecting greater problems with compliance.

The Influence of Depression on Outcome

We reanalyzed our sample's outcome variables by dichotomizing the group by either the presence or absence of a secondary diagnosis of depression by DSM-III-R criteria or a critical value of the Zung of 40 points. Results were comparable, so we report only the analysis with the DSM-III-R diagnosis.

A secondary diagnosis of major depression by DSM-III-R diagnostic criteria was applied to 8 of 27 patients with restrictive anorexia and 8 of 14 with bulimic features (χ^2 0.25, not significant). This was reduced to 6 and 4 patients, respectively, on follow-up (χ^2 0.00, not significant). By a Zung score of 40, moderate to severe depression was diagnosed in 24 of 41 patients (58%). This number dropped to 15 (37%) on follow-up. It seems that by either method of measuring depression, only a third of our depressed patients responded to the psychosocial treatment package with improvement in their moods. It also seems that depressed patients with anorexia were significantly worse off on five of seven outcome variables (Table 4).

We then repeated our original MANOVA on all the outcome variables, this time with the Zung score as a covariant. Although there was evidence for overall Zung scale differences among the groups (Roy's greatest root = 1.61, F (4,34) = 13.7, $P = .0001$), there also was evidence for additional treatment and compliance effects. The findings for a treatment effect in the three treatment groups remained significant (Roy's greatest root = 0.367, F (3,35) = 3.21, $P = .02$). Patients completing treatment were significantly better on the GCS ($P = .01$), the social adjustment portion of the GCS ($P = .008$), and the EDI ($P = .005$) but not on the EAT or the ideal body weight percentage.

TABLE 2.—*Outcome in Anorexic Groups Who Received Treotment Elsewhere**

Outcome Variable	Treatment Elsewhere: None, n = 10	Partial, n = 8	Major, n = 9	Significance
GCS†	5 ± 3.6	6.3 ± 2.3	7.3 ± 3.9	NS
Ideal body weight %†	91.5 ± 11	89 ± 11.6	89 ± 6.5	NS
Menses, Reg/Irreg/None	2/1/6	3/1/3	2/1/3	NS
GCS, Social Adjustment†	1.5 ± 1.7	1.4 ± 1.3	3.4 ± 1.7	‡
Zung†	32.5 ± 10.1	46 ± 10	42 ± 12	§
EAT†	22.3 ± 15	25 ± 13.5	33 ± 20	NS
EDI†	35 ± 20	62 ± 35	56 ± 31	NS

Irreg = irregular, NS = not significant, Reg = regular

*Higher scores on the global clinical score (GCS), the Eating Disorders Inventory (EDI), the Eating Attitude Test (EAT), and the Zung Self-Rating Depression Scale indicate more severe disease.

†Scores are given in the mean ± standard deviation.

‡Median one-way analysis: $\chi^2 = 5.9$, $df = 2$, $P = .02$.

§Median one-way analysis: $\chi^2 = 7.8$, $df = 2$, $P = .02$.

TABLE 3.—*Comparison of Outcome of Anorexia With Restrictive and Bulimic Features**

Outcome Variable	Anorexia Nervosa: Restrictive, n = 27	Bulimic, n = 14	t	P
GCS†	4.5 ± 2.7	6.7 ± 3.8	2.15	.04
Ideal body weight %†	88 ± 10	93.4 ± 6.5	1.9	NS
Menses, Reg/Irreg/None	7/4/14	5/2/4	2.9	NS‡
GCS, Social Adjustment†	1.1 ± 1.4	2.7 ± 1.5	3.3	.002
Zung†	37 ± 10	43 ± 10	1.94	.06
EAT†	24 ± 17	24 ± 17	0.07	NS
EDI†	36 ± 28	56 ± 34	2.1	.05
EDI minus bulimia subscale†	34 ± 2	52 ± 31	2.0	.05
Treatment categories, Inc/Major/Complete	6/8/13	6/7/1	7.0	.03‡
Major depression as secondary diagnosis	19/8	8/6	0.03	NS‡

Inc = incomplete, Irreg = irregular, NS = not significant, Reg = regular

*Higher scores on the global clinical score (GCS), the Eating Disorders Inventory (EDI), the Eating Attitude Test (EAT), and the Zung Self-Rating Depression Scale indicate more severe disease.

†Scores are given as the mean ± standard deviation.

‡Analysis by χ^2.

TABLE 4.—*Comparison of Outcome in Anorexic Adolescents With and Without Secondary Diagnosis of Major Depression by DSM-III-R Criteria*†*

Outcome Variable	With Depression, n = 14	Without Depression, n = 27	t	P
GCS	7.0 ± 3.1	4.4 ± 3.0	2.15	.01
Ideal body weight %	90 ± 9	89 ± 9	0.33	NS
Menses, Reg/Irreg/None	3/2/6	9/4/12	2.0	NS‡
GCS, Social Adjustment	2.3 ± 1.9	1.4 ± 1.4	1.8	.08
Zung†	48 ± 9	34 ± 8	4.8	.000
EAT†	36 ± 20	18 ± 12	3.6	.001
EDI†	68 ± 32	28 ± 20	4.8	.000
Treatment Categories, Inc/Major/Complete	5/5/4	7/10/10	0.5	NS‡

DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised,[26] Inc = incomplete, Irreg = irregular, NS = not significant, Reg = regular

*Higher scores on the global clinical score (GCS), the Zung Self-Rating Depression Scale, the Eating Attitude Test (EAT), and the Eating Disorders Inventory (EDI) indicate more severe disease.

†Except for Menses, scores are given as the mean ± standard deviation.

‡Analysis by χ^2.

When we repeated this MANOVA with only the groups who had received treatment in other settings, there was a significant overall difference (Roy's greatest root = 0.852, F (4,21) = 6.5, P = .009). The group that had the most favorable outcome, however, was the one that had no further intervention. Furthermore, the only significant difference on specific outcome variables was on the social adjustment portion of the global clinical score (P = .008). All other differences—GCS, EDI, EAT and ideal body weight percentage—were not significant.

Outcome by Depression and Bulimic Features

Splitting the sample into groups based on the presence or absence of bulimia and depression, there were no significant differences on global clinical score, ideal body weight percentage, menses, and treatment completion, but the EDI, EAT, and the social adjustment ratings on the GCS were significantly different. Depression seems to most adversely influence psychopathology (EAT and EDI). Bulimia seems to influence mostly social adjustment and, possibly, treatment completion (Table 5).

Discussion

Our hypotheses were generally supported, but there were some important exceptions with respect to depression and bulimic behavior.

The outcome in the total sample is comparable to that reported in other treatment programs.[1-8,12-25] The fact that there were no deaths is probably due to our close medical supervision and the age of the sample. The difference in readmission to hospital rates between patients with bulimia and those with restrictive anorexia most likely reflects the former's problems with electrolytes and fluids that present as life-endangering emergencies. Spontaneous recovery seems to be rare (5%), having occurred in only one patient with a treatment score of 0 and another with a treatment score of 1. This rate is comparable to that reported by Vandereycken and Pierloot.[1] One of our patients had restrictive anorexia, the other a bulimic subtype; neither of them had a secondary diagnosis of depression.

Compliance with treatment was better than we expected and somewhat better than reported by Vandereycken and Pierloot.[1] Of the 27 patients who did not complete our program, 17 did go on to seek treatment elsewhere. In all, 9 seemed to complete their course of treatment, thus bringing the number of total compliance in 50 patients to 23 (46%). Only 3 of 41 patients (7%) refused any treatment altogether, either with us or elsewhere; 15 (37%) received at least some intervention, either with us or elsewhere. These percentages are not too different from findings in the treatment of other illnesses.[9,10] Patients suffering from anorexia seemingly are no worse a risk for noncompliance than other patients, at least in the adolescent age range. As the length of illness becomes more protracted and wearing, this favorable picture may change dramatically, an issue well worth further investigation. Also of interest was that patients with restrictive anorexia were more compliant with treatment, at least initially, while those with bulimic features had a much higher dropout rate. No other baseline variable predicted this. Because compliance rates for patients with bulimic and restrictive anorexia were comparable in subsequent treatment programs, it is possible that this phenomenon represents the bulimic anorexic patients' dissatisfaction with our program, which did not treat bulimic behavior in any specific way. We conceptualized bulimic symptoms as a by-product of starvation and reasoned that they would decline as weight rehabilitation proceeded. We subsequently revised this approach and now address bulimic symptoms in specific protocols. On the other hand, bulimic and restrictive anorexic patients' different patterns of engaging in treatment may have more general significance and relate to the patients' differing ways of forming treatment alliance or to more or less well-functioning families who see to it that treatment prescriptions get carried out.[3,4,6,12,15]

Although depression at diagnosis does not predict compliance initially, it does predict who will seek further treatment after the initial dropout. Depression, which is usually accompanied by more severe symptoms, does not seem to permit spontaneous recovery or recovery after minimal intervention but seems to lead patients to further treatment.

When the effects of completing the initial treatment program at Children's Hospital were examined, significant differences were noted between the groups on three of the four major outcome variables—GCS, EAT, EDI—but not in terms of depression. With some of the components of the GCS, the groups all fared equally well in terms of weight and menses. Differences manifest themselves on more subtle measures of general and specific features of eating disorders. This argues for the inclusion of such measures in future studies. Although the groups are almost identical in terms of weight and menstrual status, those who completed treatment could be less at risk for relapse in the years to come, most notably as they leave their families of origin. The exclusion of these measures might help explain the findings of Agras and Kraemer that there seem to be no specific treatment effects evident in anorexia nervosa.[24]

TABLE 5.—*Outcome by Depression and Bulimic Features**†

	Type of Anorexia Nervosa					
Outcome Variable	*Restrictive, Not Depressed, n = 19*	*Restrictive, Depressed, n = 8*	*Bulimic, Not Depressed, n = 8*	*Bulimic, Depressed, n = 6*	χ^2	P
GCS‡	3.8 ± 2.5	6.1 ± 2.6	5.8 ± 3.8	8 ± 3.6	5.6	NS
Ideal body weight %‡	88 ± 10	88 ± 10	93 ± 7	94 ± 6.7	2.5	NS
Menses, Reg/Irreg/None	5/3/9	2/1/5	4/1/3	1/1/1	12.5	NS
GCS, Social Adjustment‡	1.1 ± 1.3	1.4 ± 1.7	2.1 ± 1.5	3.5 ± 1.4	11.4	.009
EAT‡	17 ± 12.5	39 ± 19	19 ± 13	31 ± 21	8.6	.04
EDI, minus bulimia subscale‡	25 ± 21	57 ± 24	35 ± 15	75 ± 34	15.5	.001
Treatment categories, Inc/Major/Complete	4/6/9	2/2/4	3/4/1	3/3/0	7.4	NS

Inc = incomplete, Irreg = irregular, NS = not significant, Reg = regular

*Higher scores on Garfinkel global clinical score (GCS), Eating Disorders Inventory (EDI), Eating Attitude Test (EAT), and Zung Self-Rating Depression Scale indicate more severe disease.

†Analyses by either χ^2 or median one-way analysis.

‡Scores are given as the mean ± standard deviation.

Our findings are also in line with those of Isager and associates that treatment beyond a year significantly reduced the risk for relapse.[2] Although the groups did not differ on several important variables at the outset, the distribution of restrictive and bulimic characteristics confounds our analysis, thus making it impossible to claim the specific effects of our treatment without examining those of treatment elsewhere.

These post hoc analyses suggest that either patients who complete the initial program have some favorable characteristics not measured in our assessment, or that our program is particularly effective with patients with restrictive anorexia. Subsequent treatment produced no significant differences on any of the major outcome variables (GCS, EDI, EAT), and those who received no further treatment at all had the most favorable outcome on all variables. Compared with the group who initially completed treatment, all three groups look less favorable; the one group closest to those completing treatment is the one with no further treatment. This suggests that patients who drop out initially are at a higher risk for a more protracted course, are less responsive to further treatment, and are probably at a higher risk for relapse. The presence of bulimic symptoms seems to confer greater morbidity, even when the added weight for bulimic symptoms is corrected for in the measurements. This finding is in line with several investigations[3,17,22,25] but not others.[12] The problems are not confined to specific eating problems but reflect general adjustment as well. In their study, Toner and colleagues found no differences among anorexic subgroups after seven years.[12] Our follow-up period is only half theirs, so it is possible that ultimately patients with bulimic features will become comparable to those with the restrictive subtype. Conversely, these features may be of different prognostic importance in adolescents.

Our findings of depression in a sizable portion of these patients replicates those from other studies in this adolescent population.[17,25,34] These mood problems do not resolve with the refeeding process, predict higher morbidity on follow-up, and are less responsive to treatment subsequent to initial treatment dropout. The use of antidepressants in patients with persistent mood disturbance after refeeding is recommended. When we repeated our initial between-treatment group analyses, using the Zung scores as a covariant, we still found a significant effect of treatment completion on outcome. Differences still favored those completing treatment. By contrast, when the same analysis of covariance between groups who had received treatment in other settings after dropout at Stanford was done, no such differences were detected. This suggests that our program may have specific effects that merit exploration in a controlled design.

When the possible differential effects of bulimic symptoms and depression are examined, our results suggest different influences. Depression seems to increase the self-report of an eating disorder, while bulimia worsens social adjustment, even when the weighing of bulimic symptoms is corrected. Depression seemingly increases "internalizing" symptoms (self-described suffering), but bulimia is more likely to be accompanied by "externalizing" symptoms (maladjustment readily observable by others).

The limitations of our study include a relatively small sample size, the relatively short duration of follow-up, and a lack of baseline data on one of the outcome measures.

Our results confirm the importance of reporting treatment compliance in outcome studies before judging the effectiveness of a treatment approach. It underlines the importance of a multimodal assessment beyond weight to achieve a complete picture of the effects of treatment. Presumably, weight gain accompanied by the correction of distorted attitudes is of better prognostic value than weight gained without such changes. Bulimic behavior needs special targeting beyond weight gain and psychotherapy.

Finally, depression does not seem to respond to psychosocial treatment alone and seems to contribute to a poor prognosis. Some of these patients might be better helped by psychopharmacologic intervention.

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Articles

The Changing Epidemiology of Diabetes Mellitus Among Navajo Indians

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Although early descriptions of diabetes mellitus among Navajo Indians characterized the disease as an infrequent and "benign chemical abnormality," the prevalence of diabetes and its complications among Navajos appears to have increased substantially in this century. We reviewed recent Indian Health Service inpatient and ambulatory care data and compared these data with previous reports. Of the estimated Navajo population aged 45 years or older, 4,331 (16.9%) had an ambulatory care visit for diabetes between October 1, 1986, and September 30, 1987. Diabetes was coded for 1,041 (7.0%) of hospital admissions of persons aged 20 and older. Of 377 lower-extremity amputations done from 1978 to 1987, diabetes was involved in 245 (66%). The 1986 age-adjusted mortality rate from diabetes was 30.3 per 100,000, approximately twice that for the general US population. The explanation for the increased prevalence of diabetes mellitus among Navajos probably relates to an increasing prevalence of obesity.

(Sugarman JR, Hickey M, Hall T, et al: The changing epidemiology of diabetes mellitus among Navajo Indians. West J Med 1990 Aug; 153:140-145)

Non-insulin-dependent diabetes mellitus (NIDDM), a disease that was previously uncommon among Native Americans, has become a major health concern in many American Indian communities.[1] The rising prevalence of diabetes and its complications has been well documented among the Pima Indians of southern Arizona, the tribe that has received the most extensive investigation.[2-4] Studies among the Pimas suggest that environmental influences resulting in increased rates of obesity superimposed on a genetic susceptibility to the disease have contributed to the increased prevalence of diabetes among American Indians.[5]

Although early descriptions of diabetes among members of the Navajo Tribe, the largest tribe in the United States, characterized the disease as a "benign chemical abnormality" rarely accompanied by vasculopathy,[6,7] more recent studies have found that diabetic Navajos are not spared from the typical vascular complications of diabetes.[8-10] Nevertheless, a belief persists that diabetic complications remain uncommon among Navajos, and earlier reports are still cited as evidence that Navajos are somehow protected from the sequelae of long-standing diabetes.[11]

To provide a historical perspective on the changing epidemiology of diabetes among the Navajos, we reviewed recent Indian Health Service (IHS) records regarding diabetes among Navajo Indians and compared these data with those of previous reports.*

The Navajo Tribe

Approximately 180,000 members of the Navajo Tribe reside on a 25,000-sq mi reservation in the southwestern United States. The Navajos are culturally and genetically distinct from many other southwestern tribes. Whereas the Pimas descended from the Mesoamerican Hohokam cultural group and the Pueblo and Hopi tribes from the Anasazi (a separate Mesoamerican cultural group), anthropologists think that the Navajos descended from Athapaskan peoples who migrated from the north in the 16th century.[12] The recent history of the Navajo people has been marked by a transition from a primarily agrarian life-style of sheep herding and subsistence farming to a wage economy based on the reservation's abundant natural resources.[13,14] The Navajo population grew from about 88,000 in 1965 to more than 176,000 in 1987 (Indian Health Service, Office of Program Statistics, Rockville, Md). As a result, the Navajo population is younger than the general United States population; more than half the Navajo population is younger than 20 years.[14] Despite changes in the demography of the population, however, the traditional language, religion, and medicine remain as powerful influences in contemporary Navajo culture.[15,16]

Health care on the Navajo Reservation is provided primarily by the IHS, an agency of the United States Public Health Service. In the Navajo Area, a division of IHS serving most reservation residents, care is provided at 6 hospitals, 7 ambulatory health care centers, and 12 smaller health stations organized geographically into 8 Service Units. Services are provided at no charge in accessible locations across the reservation as shown in Figure 1. Selected patients are referred to surrounding community facilities for specialized care. In addition, some Navajos seek primary care from private facilities on or adjacent to the reservation. No data system exists that can estimate the proportion of Navajo patients who seek care exclusively outside the IHS system, but this proportion is thought to be low because the number of registered patients at Navajo Area IHS facilities is about equal to population estimates derived from census data.

Methods

The IHS collects demographic and clinical information on all outpatient visits and hospital admissions at IHS facilities. In addition, records are maintained for hospital admissions at non-IHS facilities that are reimbursed by the

*Stephen Kaufman, Ron Meeks, and Aaron Handler of the IHS Office of Program Statistics and Michael Everett, PhD, and Ruby Spencer of the Navajo Area IHS Office of Program Planning provided us with data from IHS records.

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The opinions expressed in this paper are those of the authors and do not necessarily reflect the views of the Indian Health Service.

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ABBREVIATIONS USED IN TEXT

FY = fiscal year
ICD = International Classification of Diseases
IHS = Indian Health Service
NIDDM = non-insulin-dependent diabetes mellitus

IHS Contract Health Service Program. Services performed at Veterans Administration facilities or admissions to a hospital off the reservation that are funded through third-party sources such as Medicaid are not included in the present data. Many patients are transferred back to IHS facilities before their final hospital discharge, however. Residents of the outlying Navajo communities of Alamo, Canoncito, and Ramah are included in this analysis only if they presented for services at Navajo Area hospitals.

All outpatient visits between October 1, 1986, and September 30, 1987 (fiscal year [FY] 1987), for which diabetes mellitus was listed as one of two possible diagnoses were identified. Because the same person may seek care at more than one facility, and medical record numbers are different at different sites, a method was developed to differentiate persons with diabetes. Records were sorted by sex, community of residence, and date of birth; those matching on all characteristics were counted as one diabetic person. The proportion of Navajo IHS beneficiaries with diabetes in selected age groups was then calculated. Population estimates were derived from the 1980 census and projected to 1987 by the IHS (Office of Program Statistics, Rockville, Md).

All hospital records from Navajo Area IHS facilities for FY 1987 listing diabetes (International Classification of Diseases, revised [ICD-9], codes 250.0 to 250.9)[17] as one of six possible discharge diagnoses were selected. Cases of lower-extremity amputations (ICD-9 codes 84.1 to 84.19, or ICD-8 codes 85.5 to 85.9) were identified among all Navajo Area IHS hospital discharges from October 1, 1978, to September 30, 1987 (FY 1979 to FY 1987), from surgical procedures coded at discharge. All hospital discharges for lower-extremity amputations listing a discharge diagnosis with ICD-9 code from 250.0 to 250.9 were considered to be related to diabetes. One of us (J.R.S.) reviewed the remaining medical records of patients with amputations to ensure that diabetes had not been inappropriately omitted from the discharge diagnoses. To determine whether Navajos with diabetes were admitted to hospital with the usual complications of diabetes found in other populations, the number of hospital admissions for selected complications associated

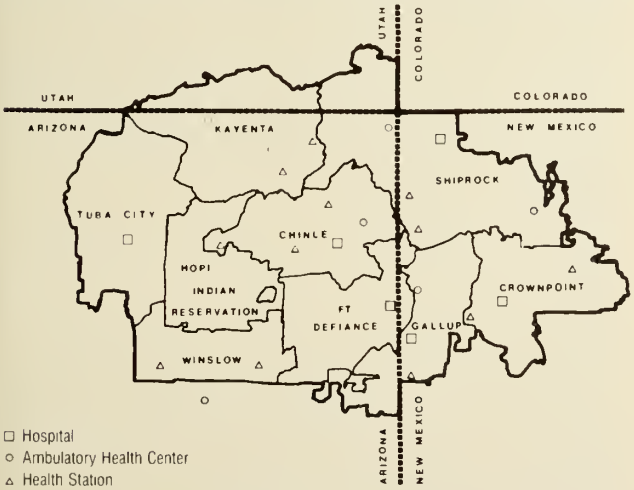

Figure 1.—The map shows the location of Navajo Area Indian Health Service health care facilities.

TABLE 1.—*Selected Diagnoses for Persons With Diabetes Discharged From Navajo Area IHS Hospitals,*† October 1, 1986-September 30, 1987*

Discharge Diagnosis (ICD-9 code)	*Patients, No.*
Acute and chronic ischemic heart disease (410-414)	96
Renal failure, nephropathy, nephrosis, diabetes with renal manifestations (581, 583, 585, 586, 250.4)	53
Cellulitis, abscess, and other skin infections (681, 682, 686)	64
Chronic ulcer of skin (707)	28
Osteomyelitis, periostitis, and other infections of bone (730)	19
Gangrene (785.4)	35
Ketoacidosis or hyperosmolar coma (250.1, 250.2)	49
Hypoglycemia (251.0, 251.2)	17

IHS = Indian Health Service

*Only the first or second of six possible diagnoses are included.
†All discharge diagnoses have International Classification of Diseases (ICD-9) codes 250.0 to 250.9.[17]

with diabetes among persons admitted in FY 1987 was determined. These complications are reported only if diabetes was coded as one of six possible discharge diagnoses and if the complication was the primary or secondary discharge diagnosis.

A roster of diabetic patients who received care from the Shiprock Service Unit is maintained on a microcomputer at the Shiprock Public Health Service Hospital, a 50-bed inpatient and ambulatory care facility with a catchment population of about 40,000. The roster was compiled using data from outpatient visits and hospital discharge records, as well as from attendance records from the Shiprock Hospital Diabetes Clinic. The year of diagnosis as recorded in the medical record is included in the roster. The year of diagnosis for patients included in the roster as of January 1988 is presented in this report.

The death certificates of American Indians are made available to the IHS by the National Center for Health Statistics. The mortality rate for diabetes as the underlying cause of death (as recorded on death certificates) for deaths occurring in the Navajo Area for 1986 was calculated and age-adjusted by the direct method to the 1980 US population.* This mortality rate was compared with that in the general US population in 1986, age-adjusted to the same population.[18]

Results

A diagnosis of diabetes mellitus was recorded for 26,343 (3.9%) of 679,990 ambulatory care visits to Navajo Area IHS facilities in FY 1987. Of the estimated 176,321 Navajos residing on the Navajo Reservation, 5,710 (3.2%) received a diagnosis of diabetes during an ambulatory care visit at a Navajo Area facility. Of the 25,616 persons aged 45 years and older, 4,331 (16.9%) received a diagnosis of diabetes. There were 20,491 admissions to Navajo Area hospitals during the same period. Navajo tribal affiliation was recorded for 19,165 (93.5%) of those admissions. After hospital admissions for childbirth and the puerperium are excluded, 13,738 admissions remained. A discharge diagnosis of diabetes (ICD-9 code 250.0 to 250.9) was recorded for 1,048 (5.1%) of the total admissions, or 7.6% of admissions excluding those for childbirth and the puerperium. There were seven patients younger than 20 years, and three of these were designated as members of tribes other than Navajo according to the IHS records system. When patients younger than 20 years were excluded, diabetes was coded

*Sarah Valway, DMD, MPH, assisted with data analysis.

TABLE 2.—*Hospital Discharges for Amputations, Navajo Area IHS Hospitals, FY 1978-1987**

Year	Total Amputations No.	Amputations in Diabetic Persons, No.	Amputations in Nondiabetic Persons, No.	Proportion of Amputations in Diabetic v Nondiabetic Persons, %	Total Amputations/ 10,000 Navajo Population
1978	36	20	16	55.6	2.75
1979	50	16	34	32.0	3.61
1980	37	28	9	75.7	2.55
1982	42	26	16	61.9	2.74
1983	47	32	15	68.1	2.98
1984	48	33	15	68.8	2.96
1985	38	26	12	68.4	2.28
1986	31	26	5	83.9	1.81
1987	48	38	10	79.2	2.72
1978-1987*	377	245	132	65.0	

IHS = Indian Health Service

*Excluding 1981, for which complete data are not available.

for 1,041 (7.0%) of 14,986 admissions. Of 1,975 admissions to hospitals reimbursed by the IHS Contract Health Service Program, 87 (4.4%) were accompanied by a diagnosis of diabetes. The number of patients discharged from Navajo Area IHS hospitals with selected discharge diagnoses recorded as the first or second of six possible diagnoses that are directly related to diabetes, or for which diabetes is a risk factor, is displayed in Table 1.

From FY 1978 to FY 1987 (excluding FY 1981 for which data were not available), diabetes was associated with 245 (66%) of the 377 lower-extremity amputations carried out in Navajo Area IHS hospitals. The proportion of amputations in persons with diabetes, by year, is presented in Table 2. The FY 1987 amputation rate of 66.5 per 10,000 patients with diabetes is similar to the estimated rate of 59.7 per 10,000 people with diabetes in the United States.[19]

The year of the diagnosis of diabetes among 1,265 persons with diabetes listed on the Shiprock Service Unit Diabetes Registry is presented in Figure 2. Although these data do not represent annual incidence rates, they suggest that the number of Navajo Indians with diagnosed diabetes is increasing at a rapid rate.

The 1986 age-adjusted mortality rate for diabetes as the underlying cause of death in the Navajo Area was 30.3 per 100,000, compared with 15.4 for the general US population.

Comment

These data provide compelling evidence that the epidemiology of diabetes mellitus among Navajo Indians has changed dramatically during this century. Indeed, from the earliest published data regarding the proportion of diabetes-related hospital admissions among Navajos (Table 3), there were only 5 patients with diabetes out of 25,000 admissions to Sage Memorial Hospital in Ganado, Arizona, between 1931 and 1947.[20,21] In 1940 the pioneering diabetologist, Elliott Joslin, MD, reported the results of an extensive survey of diabetes in Arizona during which he was able to identify only four cases of diabetes in Navajo Indians.[22] Between 1950 and 1952, only 0.6% of Navajos and Hopis admitted to the Phoenix Indian Medical Center had diabetes,[23] a rate that increased to 1% between 1958 and 1965.[24]

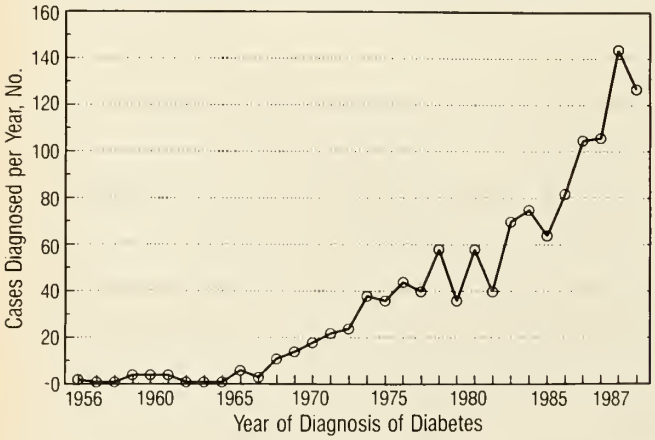

Figure 2.—The year of diagnosis is shown for persons with known diabetes mellitus, Shiprock Service Unit, Navajo Area Indian Health Service, 1987.

It appears that the prevalence of diabetes among Navajos had begun to increase by the 1960s. Among patients discharged from the Fort Defiance (Arizona) Hospital from 1958 to 1963, diabetes was reported to be present in 0.91% of those older than 20 years and 2.3% of those older than 45.[6] Between 1963 and 1965, diabetes was identified in 78 Navajos among hospital and clinic patients at the Tuba City Hospital, which served approximately 15,000 Navajos at that time.[7] In 1971 in a small survey of Navajos aged 35 and older in the Fort Defiance area, 12.8% had carbohydrate intolerance as identified by a plasma glucose concentration of 8.88 mmol per liter (160 mg per dl), or higher, two hours after a 75-gram carbohydrate load.[25] Using a two-hour postprandial plasma glucose concentration of 11.1 mmol per liter (200 mg per dl), or higher, the prevalence of diabetes in that population was 11.1% (Peter Bennett, MB, FRCP, FFCM, and Cheryl Ritenbaugh, PhD, MPH, written communication, July 1989). A recent community-based study among Navajos yielded a diabetes prevalence of 10.2% of those between the ages of 20 and 74 (compared with 6.4% in the general US population) and 19.5% among those between the ages of 45 and 74 (compared with about 13% in the general US population).[26]

The explanation for the increasing prevalence of diabetes and its complications among Navajos is complex. Although it is likely that earlier studies suffered from incomplete case ascertainment, it is doubtful that the diagnosis of diabetes would have been completely overlooked in patients with blindness, renal insufficiency, lower-extremity gangrene, and ischemic heart disease. Increased survivorship among persons with diabetes may account for the rising prevalence of diabetes, as the average life expectancy of Navajo people has increased from 64.9 years in 1973[27] to 71.1 years in 1980 (Office of Program Planning and Development, Navajo Area IHS, Window Rock, Arizona, 1986).

TABLE 3.—*Rates of Diabetes Mellitus Among Navaja Indians, 1937-1989*

Reference	*Populotion*	*Years of Study*	*Age of Population, Years*	*Percent (and number) With Diabetes*
Salsbury, 1937 and 1947[20,21]	Inpatients, Sage Memorial Hospital, Ganado, Ariz	1931-1947	All	0.02% of admissions (5/25,000)
Joslin, 1940[22]	Navajo Indians, Ariz	1940	All	< 0.01% of population (4/approximately 50,000*)
Cohen, 1954[23]	Inpatients, Phoenix Indian Medical Center	1950-1952	All	0.6% of Navajo admissions (NA)
Sievers, 1966[24]	Inpatients, Phoenix Indian Medical Center	1958-1965	≥ 20	1% of Navajo admissions (NA)
Saiki and Rimoin, 1968[6]	Inpatients, Fort Defiance Hospital, Fort Defiance, Ariz	1958-1963	All	0.6% of admissions (105/17,557)
			> 20	0.91%
			> 45	2.3%
Prosnitz and Mandell, 1967[7]	Outpatients and inpatients, Tuba City Hospital, Tuba City, Ariz	1963-1965	All	0.052% of Navajos in hospital catchment area (78/15,000†)
Sugarman and Percy, 1989[26]	Community based, Teec Nos Pos, Ariz	1986-1987	20-74	9.9% of population (44/444)
			45-74	19.5% (37/190)
Current study	All Navajo Area Indian Health Service Facilities	1986-1987	All	5.1% of admissions (1,048/20,491)
				3.2% of outpatients (5,710/176,321 population)
			≥ 20	7.0% of admissions (1,041/14,986)
			≥ 45	16.9% of outpatients (4,331/25,616)

NA = not available

*Navajo population in 1940 as estimated by Kluckhohn and Leighton.[13]

†There were approximately 70,000 outpatient visits and 5,000 hospital admissions during the study period (Office of Program Statistics, Indian Health Service, Rockville, Md).

Accurate life expectancy data for Navajos before 1973 are not available, although the mortality rate for both children and adults appears to have fallen continuously from the early 1900s to the 1970s.[28(p61)] Infectious diseases such as tuberculosis, which was previously epidemic among Navajo Indians, may have shortened the survival of diabetic Navajos before the introduction of effective chemotherapy.[29] Diabetic Indians admitted to hospital in the 1950s had more severe tuberculosis than their nondiabetic counterparts.[23]

A more plausible explanation for the increased prevalence of diabetes is that the prevalence of obesity, a major risk factor for NIDDM, among Navajo Indians has increased substantially during this century. Several reports suggest that an increase in the prevalence of obesity has occurred in parallel with the epidemic of diabetes. In a 1955 survey of weight and stature among 1,200 Navajos, only 5% of male Navajos and less than 15% of female Navajos were obese as measured by a 1939 "percent of standard weight" criterion.[30] The Navajo-Cornell Field Health Study reported that 11% of men and 20% of women among 406 volunteers aged 30 and older were obese by an ideal weight standard, although the specific standard was not mentioned.[31] In 1979, however, 24% of men and 51% of women in a broad sample of Navajos were found to be greater than 110% of the upper limit of optimal weight for height according to the 1959 Metropolitan Life Insurance tables.[32] In a recent study using the National Health and Nutrition Examination Survey (NHANES I) body mass index criterion for overweight, 42.1% of Navajo men and 54.7% of Navajo women aged 20 to 74 were overweight compared with 22.8% and 29.5%, respectively, of men and women in the general US population.[26] Despite the variations in the definition of obesity in these studies, there is little doubt that the number of Navajos described as obese has increased during the past 30 years.

This increase in obesity may be attributable in part to the greater availability of calorie-dense food through government commodity food programs and to more access to centers of commerce where "fast foods" and prepared foods of poor nutritional quality are easily available. Although no recent systematic surveys of Navajo dietary habits have been done, high levels of caloric consumption, especially of refined carbohydrate, fat, and sodium, have recently been noted in the Navajo.[14] Reduced physical activity may also play a role. Until recently, daily subsistence activities and transportation needs required moderate to heavy energy expenditure.[31,33] The notion of a "thrifty gene" conferring the ability to store calories in times of plenty and release them in times of famine has been proposed to explain the recent increase in obesity and diabetes among other tribes.[5,34,35] According to this hypothesis, such a gene might confer an evolutionary advantage in cultures susceptible to alternating periods of feast and famine but would be rendered dysfunctional in uninterrupted times of plenty because of the propensity to become obese. Although no evidence exists to give support to the presence of such a gene among Navajos, it is possible that the recent increase in obesity is partially mediated by a heritable factor.

There are several limitations to the estimates of diabetes mellitus made from the ambulatory care and inpatient diagnoses in the present study. A recent review of a random sample of the medical records of Navajo Area IHS patients who were recorded as having an ambulatory visit for diabetes revealed that approximately 13% of the patients did not have diabetes (J.R.S., unpublished data, 1989). The errors were primarily due to an inappropriate coding of testing for diabetes in patients who were not found to have diabetes and to a simple miscoding of unrelated diagnoses. Thus, the above figures overestimate the number of diabetic persons who sought care at Navajo Area IHS facilities during FY 1987. On the other hand, because not all persons with diagnosed diabetes seek care during a given fiscal year, the total number of Navajos with known diabetes may be underestimated by evaluating visits for only one fiscal year. Furthermore, it is likely that a substantial reservoir of undiagnosed diabetes exists among the Navajo population. Thus, the actual prevalence of the disease is likely to be higher than that suggested from reviews of medical records.

Because only the first two of six possible diagnoses were analyzed for Table 1, it is likely that the number of admissions for the complications listed was underestimated. In addition, the total number of hospital admissions for diabetes was probably underestimated, as more than 10% of amputations in diabetic patients were not so identified in the hospital admission data set but were recorded on the medical record review. Although it is likely that some of the

conditions noted in Table 1 are unrelated to diabetes, the large number of hospital admissions for the specific complications of diabetes confirm that Navajos with diabetes suffer from the typical microvascular and macrovascular complications of the disease.

These data are consistent with those of several recent studies regarding diabetic complications among Navajos. Diabetes was present among 21 (34%) of 61 Navajos sustaining myocardial infarction from 1976 through 1979, a proportion that had increased to 78 (50%) of 157 cases by the interval from 1984 to 1986.[10] The incidence of end-stage renal disease caused by diabetes among Navajos is almost 10 times that in the general US population.[9] High rates of retinopathy have also been reported.[8] Earlier authors, however, were impressed by the lack of vascular complications among Navajos with diagnosed diabetes.[6,7] The discrepancy between the observations from the 1960s and those from the 1980s can be at least partially explained by a differing duration of diabetes among the two cohorts. The diabetic patients observed in the earlier reports did not present with diabetes of a long duration. For example, the duration of diagnosed diabetes was more than 10 years in only 5% of the population of Hopis and Navajos studied by Prosnitz and Mandell from 1963 to 1965,[7] whereas in 1980 Rate and co-workers found that 24% of Navajos in a nearby community had diabetes of 10 years or longer.[8] In that study, the mean duration of diabetes in patients with vascular complications was 12.4 years compared with 6.9 years in those without complications. The increasing frequency of complications such as retinopathy and nephropathy with increasing duration has been described among the Pimas and among non-Indian populations.[2,36] Of the patients described in Figure 2, a total of 388 (30.7%) had diabetes of 10 or more years' duration. Thus, it is likely that many patients in previous studies did not have diabetes of a sufficient duration to manifest the typical vascular complications.

Type I or insulin-dependent diabetes mellitus is reported to be rare among American Indians,[37] yet we identified ketoacidosis as a reason for being admitted to hospital. Ketoacidosis may occur in persons with NIDDM, especially in those who drink alcohol to excess.[38,39] Therefore, our data should not be used to argue that type I diabetes occurs among the Navajo. Indeed, the paucity of hospital admissions for diabetes in persons younger than 20 years is consistent with previous observations about the rarity of type I diabetes among American Indians.

The epidemic of diabetes among the Navajo has implications for other Americans. Alaskan Inupiaqs and Yupiks (Eskimos), Indians, and Aleuts have a lower prevalence of diabetes than the general US population, but there is evidence to suggest that the prevalence of diabetes in those populations is rising.[40] Because Navajos are closely related to the Athapaskan Indians of Alaska, vigorous prevention efforts should be directed toward obesity control in that population. The prevalence of known diabetes among African Americans tripled between 1963 and 1985, whereas the rate among whites about doubled during the same period.[41] Hispanic Americans have a higher prevalence of diabetes than does the US white population, and the prevalence of diabetes among Hispanics increases with an increasing percentage of Native American genetic admixture.[42] Thus, a study of the progress and control of the epidemic of diabetes among Navajo Indians may provide important information for other populations as well.

Contrary to earlier beliefs, diabetes among Navajo Indians clearly is not a benign form of hyperglycemia. Rather, the typical vascular complications of the disease are important causes of morbidity and mortality among Navajos. The reported prevalence of the disease has increased substantially in the past half-century, probably because of a parallel increase in obesity. To decrease the consequences of diabetes among Navajo Indians, current diabetes control activities should focus on obesity control, early diagnosis and treatment of diabetes, and vigorous monitoring for complications in diabetic patients.

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Book Review

***The Western Journal of Medicine* does not review all books sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.**

California Physician's Legal Handbook—1990

Catherine I. Hanson, Astrid G. Meghrigian, Alice P. Mead, and John H. Gilman, California Medical Association. Sutter Publications, Inc, PO Box 7690, San Francisco, CA 94120-7690. 600 pages, spiral bound; $85, CMA members; $185, nonmembers.

California physicians have long needed a legal handbook for their own guidance to avoid having to make calls to medical societies or to their attorneys for every little issue that arises in practice: How do I dismiss a patient from my care legally and amicably? How do I transfer a patient from one hospital to another? How do I deal with investigations by a medical licensing board? How do I establish and charge fees for being an expert witness? All of these questions are covered by the *Colifornio Physicion's Legal Hondbook*. This handbook can become your consultant.

A whole section covers the current reasoning behind our ability to let patients forgo treatment. Of particular importance is the material directly related to the durable power of attorney for health care. All physicians should become familiar with this document and should use it for their own lives as well as having copies available for their patients. The handbook will help you learn how to use the document.

Some problems do not have easy answers. For instance, how long should medical records be kept? The usual response is at least a bit longer than the statute of limitations for malpractice litigation, which means more than three years after the last treatment for adults. Because these statutes are not always reliable, however, the better course of action is to keep all records for a minimum of 10 years after the last time the patient was seen, or at least until the minor has become 19 years of age—provided the child had not been seen in the previous 10 years. With an abundance of caution, the handbook suggests an across-the-board retention of 25 years after the last treatment.

Who can legally determine competency for consent purposes? This is regularly asked during Ethics Rounds at the University of Southern California School of Medicine, and the answer is not always obvious. Many think that only courts can decide the issue of competency. Others believe only psychiatrists can answer that question. In reality, clinicians do it every day. It involves two questions: Can the patient understand the nature and consequences of his or her condition and the proposed treatment, and can the patient communicate his or her decision? This does not require a psychiatric diagnosis or assessment, and the people preparing the handbook were smart enough to state that very clearly. They also go on to advise that where the issue is a close one, a physician needs to talk to the people surrounding the patient—family, friends, other physicians caring for the patient, and anyone else personally familiar with the patient and available to discuss the problem. This section in the handbook is particularly well drafted.

The presentations in this handbook go beyond the strict statement of the law. They get down to the nitty gritty of day-to-day problems physicians and their office staff face. For this reason the handbook will be of immense value. It will be updated annually.

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Articles

Neurologic Complications of Cardiac Transplantation

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Between 1984 and 1989, orthotopic cardiac transplantations were done in 90 patients from 10 to 65 years of age for end-stage, refractory congestive cardiomyopathy. Two patients had had ischemic strokes 5 months and 18 years, respectively, before transplantation. Six patients (7%) suffered acute neurologic events perioperatively. Three patients suffered cerebral infarctions. In 1 case this occurred 10 days before transplantation—probably as a result of systemic hypoperfusion—with the placement of ventricular assist devices. Two others suffered infarctions 5 and 21 days, respectively, after transplantation, each of probable embolic origin. Two patients had an acute intracerebral hemorrhage 21 and 36 days, respectively, after transplantation; both were located within the basal ganglia and subcortical regions. Both patients had moderate to severe hypertension, and in 1, renal failure and a coagulopathy developed before hemorrhage. Tremor, seizures, and an altered level of consciousness developed in 1 patient as an apparent toxic reaction to cyclosporine treatment. Only 1 patient died as a result of the neurologic complication—of an acute intracerebral hemorrhage. Three patients recovered fully, 2 partially. Only the case of drug toxicity could be directly attributed to the transplantation procedure itself. We conclude that the risk of an acute neurologic insult with orthotopic cardiac transplantation is low but may result from drug toxicity, cerebral ischemia, or hemorrhagic mechanisms.

(Andrews BT, Hershon JJ, Calanchini P, et al: Neurologic complications of cardiac transplantation. West J Med 1990 Aug; 153:146-148)

After the first human heart transplantation by Barnard in 1967,[1] there was initially high enthusiasm for, followed by a waning in the use of, cardiac transplantation as the difficulties of patient selection, graft rejection, and low survival rates became recognized.[2-4] With improved methods of immunosuppression, including the use of cyclosporine,[5-7] there has been a nearly exponential increase in the number of transplantations done worldwide.[8-10] As of 1989, a total of 9,139 orthotopic heart transplantations had been recorded by the Registry of the International Society for Heart Transplantation. In addition, there were 501 combined heart-lung transplantations and nearly 300 heterotopic heart transplantations.[10] A similar dramatic rise has occurred in the number of medical centers doing these procedures: in 1989 there were 118 transplant centers in the United States.[10]

Although the survival rate after heart transplantation has improved steadily, significant common complications remain, including graft rejection, infection, graft arteriosclerosis, malignancy, abdominal complications, and drug toxicity.[4,5,11-14] These problems have led to continued perioperative mortality of approximately 9% and a five-year survival rate of 74% to 82%.[9,10]

Less well recognized, but perhaps increasingly common, are neurologic complications associated with heart transplantation. We review the neurologic complications that have occurred over the course of 90 consecutive heart transplantations at a major metropolitan transplantation center.

Patients and Methods

Between 1984 and 1989, orthotopic cardiac transplantations were done in 90 patients for end-stage, refractory congestive cardiomyopathy. Included were 75 male and 15 female patients between 10 and 65 years of age (mean 43.5 years). The causes of cardiomyopathy are shown in Table 1. The most common was myocardial ischemia due to coronary artery atherosclerosis.

A retrospective chart review was done to delineate neurologic complications that occurred during the immediate preoperative period from those that developed over the first 60 days postoperatively. Two patients with a history of previous ischemic strokes, 5 months and 18 years, respectively, before transplantation were not included in this series. Late follow-up was carried out with all transplant recipients either directly or through their primary caretakers as part of their ongoing care, at which time the occurrence of delayed neurologic complications was noted.

Results

Six patients (7%) suffered acute neurologic events perioperatively (Table 2). Cerebral infarction developed in three patients. In one a right parietal infarction occurred ten days before transplantation after two episodes of cardiac arrest and prolonged systemic hypotension leading to the placement of ventricular assist devices. Cerebral infarction in the parieto-occipital region was probably a result of cerebral hypoperfusion. Two others suffered infarction following transplantation. In one patient right hemiparesis and aphasia began 21 days postoperatively, hours after the development of paroxysmal atrial fibrillation, suggesting a probable embolic origin. The second patient had no detectable arrhythmias or hypotension, but a sudden loss of vision developed, followed by a transient coma five days postoperatively. Magnetic resonance imaging subsequently showed bilateral abnormalities in the occipital region consistent with infarcts. A cardiac workup showed no evidence suggesting an embolic source, although emboli to the vertebrobasilar circulation were suspected. The patient was treated successfully with antiplatelet therapy alone, with eventual recovery of vision.

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Two patients suffered acute intracerebral hemorrhage 14 and 36 days, respectively, after transplantation. One was located primarily within the region of the putamen, and the other occurred within the basal ganglia and subcortical area. Both patients had intermittently severe hypertension, and renal failure, sepsis, and a coagulopathy developed in one patient before hemorrhage. In the latter patient, a mycotic aneurysm may have developed and subsequently ruptured as a result of hypertension combined with the coagulopathy.

A myoclonic tremor, seizures, and an altered level of consciousness developed in one patient, probably as a toxic reaction to high-dose cyclosporine treatment. This patient had severe impairment of renal function preoperatively as a result of congestive heart failure, but azotemia had rapidly resolved after transplantation; azotemia was mild and resolving at the time of the central nervous system dysfunction.

Two of the three patients with ischemic strokes recovered fully; the third was left with persistent dysphasia. One patient with an intracerebral hemorrhage had an incomplete recovery, and the other patient died as a direct result of the hemorrhage complicated by renal failure and a coagulopathy. The patient with a toxic reaction to cyclosporine recovered fully with a tapering in dosage of the medication.

Discussion

By far the most common complications after cardiac transplantation have been acute and chronic graft rejection[4,5,7] and infections, such as mediastinitis,[12] pulmonary abscesses, and pneumonia.[5,13] Other complications have been less frequent, including coronary graft atherosclerosis, malignant lesions related to immunosuppression,[5] abdominal complications such as gastrointestinal hemorrhage and pancreatitis,[11] and drug toxicities.[7,14,15]

Although it would seem that the hemodynamic instability, the potential for cardiac emboli, and the need for systemic anticoagulation in patients undergoing a cardiac transplantation would render the central nervous system at considerable risk for stroke and hemorrhage, such events have been infrequently reported. In a review of the experience at Stanford University Medical Center between 1968 and 1981, Jamieson and co-workers found that of 206 patients receiving heart transplants, fatal strokes occurred in only 3.[5] The details of these cases were not reported. In neither the 1987 nor 1989 registries of the International Society for Heart Transplantation were strokes listed as a cause of death after transplantation.[9,10] Indeed, only one of the six neurologic complications in our series proved to be fatal, suggesting that the actual incidence of stroke, based on mortality figures, and hemorrhage may be much higher than the reports cited suggest.

TABLE 1.—*Couses of Cardiomyopathy Among 90 Patients*

Couse	*Potients, No.*	*%*
Coronary artery disease	46	51
Idiopathic	38	42
Congenital	5	6
Rejection and retransplantation	1	1

The causes of ischemic infarctions in our series included both systemic hypoperfusion related to cardiac arrest and embolism related to atrial fibrillation. Systemic hypoperfusion and cardiac arrest have been well documented to cause ischemic cerebral infarction in characteristic distributions at the boundary zones of irrigation between major cerebral arteries, occurring primarily at the parietal and parieto-occipital regions.[16,17] Reperfusion of these regions after the restoration of the blood pressure may result in the development of hemorrhage within such infarctions.[16,17]

An embolic cause of stroke has long been described in association with atrial fibrillation.[18-20] The Framingham study reported a fivefold increase in the risk of stroke among patients with atrial fibrillation in the absence of rheumatic heart disease.[19] Aberg noted that at autopsy a left atrial thrombus was present in 15.8% of patients with atrial fibrillation.[20] In one patient from our series, infarction occurred soon after the development of this arrhythmia.

Mechanical support of the circulation has previously been associated with cerebral ischemia. Bregman and associates noted that a stroke developed in one of six patients requiring an intra-aortic balloon pump before transplantation, although the stroke occurred after transplantation and removal of the mechanical devices[21]; the cause was not determined. Griffith and colleagues described the temporary use of the Jarvik-7 total artificial heart as a so-called bridge to transplantation in six patients,[22] and although no strokes were documented, each heart contained areas of macroscopic aggregations of platelets and thrombi.

Other potential sources of cardiac emboli that may occur before or during transplantation include an enlarged and hypokinetic left atrium or ventricle with mural thrombi,[18] intraoperative air embolism at the time of insertion and removal of cardiac bypass,[16,17] and retained thrombi within the transplanted graft itself.

Intracerebral hemorrhage in one patient from our series occurred as a probable result of a coagulopathy related to renal failure and sepsis. It is possible that a mycotic aneurysm developed because of sepsis and subsequently ruptured as a combined result of hypertension and the coagulation disorder. In the second patient the only apparent risk

TABLE 2.—*Clinical Summaries for Six Patients With Neurologic Complicotions of Cordiac Transplantation*

Patient	*Age, yr*	*Cordiomyopathy*	*Complicotion*	*Time, d*	*Couse*	*Treotment*	*Outcome*
1 . . .	50	Idiopathic	MCA distribution infarction	−10	Hypoperfusion; after cardiac arrest; VAD	Supportive	Complete recovery
2 . . .	53	Ischemic	Parietal infarction	+21	Embolic; atrial fibrillation	Anticoagulation	Incomplete recovery
3 . . .	38	Idiopathic	Grand mal seizure; bilateral PCA infarctions	+5	Embolic?	Antiplatelet therapy	Complete recovery
4 . . .	41	Ischemic, Marfan's syndrome	Putaminal hemorrhage	+14	Hypertension	Supportive	Incomplete recovery
5 . . .	45	Ischemic	Basal ganglia and subcortical hemorrhage	+36	Coagulopathy, renal failure, sepsis; hypertension	Supportive	Brain death
6 . . .	23	Idiopathic	Myoclonus, seizures, altered mental state	+15	Toxic reaction to cyclosporine	Drug taper	Recovery

MCA = middle cerebral artery, PCA = posterior communicating artery, VAD = ventricular assist device

factor for hemorrhage 14 days after transplantation was hypertension. Hemorrhage occurred within the region of the putamen, the single most frequent site of intracerebral hemorrhage related to hypertension, accounting for 35% to 50% of such cases.[23]

Only one patient had an apparent toxic reaction to high doses of cyclosporine, consisting of myoclonus, seizures, and an altered level of consciousness, all of which resolved after a tapering of the cyclosporine dosage. Whereas acute and chronic renal failure has been described as the most common forms of cyclosporine toxicity,[14,15] and azotemia may result in secondary seizure activity and delirium, in our patient, renal function was severely impaired preoperatively but had rapidly improved after transplantation, and azotemia was mild and resolving when these symptoms occurred. Cyclosporine use has been reported to cause seizures in 3% to 5% of patients receiving solid organ transplants; additional central nervous system toxicity has also included tremor in 21% to 55% and headaches in 2% to 15%.[24]

It is of interest that except in the patient with cyclosporine toxicity, no complication was directly attributable to the transplantation procedure itself, but rather appeared to be more directly related to preoperative or postoperative cardiac dysfunction or hypertension, in one patient complicated by a coagulopathy. Despite the seemingly high theoretic risk of cardiac transplantation to the central nervous system, in fact the greater risk is that of the clinical setting in which the procedure is done.

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Alcohol and Trauma
An Endemic Syndrome

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Injuries are a pervasive and costly problem, and alcohol use appears to be an important risk factor for injury. We examined the blood alcohol levels and selected demographic and epidemiologic variables recorded on trauma patients by 1 trauma center for a 28-month period. A total of 2,262 trauma patients were admitted to the trauma center during this period, of whom 75% were male and 72% were injured in vehicle-related incidents. Blood alcohol levels of 2,095 patients (93%) were measured, and alcohol was present in the blood of 855 (41%). Of those patients with a blood alcohol level done, 32% had a level higher than 100 mg per dl. We conclude that the level of alcohol involvement in trauma is high and that this involvement must be addressed by the medical community and the health care system.

(Meyers HB, Zepeda SG, Murdock MA: Alcohol and trauma—An endemic syndrome. West J Med 1990 Aug; 153:149-153)

Injuries are a major public health problem. They are the fourth leading cause of death in the United States, the leading cause of death between the ages of 1 and 44, the leading cause of physician contact, and they cost approximately $100 billion each year.[1] A common factor in many types of injuries is the presence of alcohol in the blood of the injured. A growing body of literature is helping to clarify the role of alcohol consumption in both intentional and unintentional injuries.[2-9] A history of trauma has been suggested as a means of identifying habitual, heavy alcohol use.[10]

An assessment of the extent of the alcohol-related injury problem has been limited in previous studies by small numbers of patients,[5] by the population studied,[7] by restricting the time of day studied,[9] by including only one type of injury,[5,6] and by biased sampling of blood alcohol levels.[7,11]

Because of these limitations and the potential for geographic variability in alcohol use,[12] we studied the level of alcohol involvement in injuries at one trauma center in our county over a 2½-year period. The objectives included documenting the extent of alcohol involvement in serious injuries and identifying targets and strategies for prevention activities.

Our study was a cooperative effort of the County of Orange Health Care Agency and the University of California, Irvine, Medical Center (UCIMC). Orange County is predominantly urban and suburban, in southern California, and has a population of 2.2 million. The UCIMC operates the designated level I trauma center in Orange County and, as a matter of policy, has measured and recorded blood alcohol levels of nearly all adult trauma-designated patients since 1985.

Patients and Methods

A 500-bed acute care hospital, UCIMC is one of four trauma centers in Orange County. The trauma service maintains a computerized data base on all trauma patients. The Orange County Emergency Medical Service Administration has promulgated countywide trauma center triage guidelines for identifying trauma patients in the prehospital phase (Figure 1). The trauma designation was based on the mechanism of injury, vital signs, and other clinical findings. The final designation was at the discretion of the base hospital physician, who directed care in the field through radio contact with the paramedics at the scene. Approximately 97% of trauma patients treated at the UCIMC trauma center were designated as such in the field by the base hospital physician. The other 3% were not brought in by paramedics or were reclassified on arrival. Drowning, near drowning, and burns were not included in the definition of trauma.

The computerized files contained data on trauma patients admitted to the UCIMC trauma center from January 1985 through July 1987. The data from three months of 1986—October, November, and December—had not been entered into the computer at the time of this study and are not included. Monthly totals were available for the three-year period from January 1985 through December 1987.

The following variables were tabulated from the data base: total number and median age of trauma patients; total number of trauma patients by month, day of the week, and hour of the day; number of male and female patients; age of trauma patients by five-year categories; type of incident (Table 1); distribution of patients by Injury Severity Score (ISS)[13]; number of patients admitted to the intensive care unit (ICU); and number of deaths. Each variable was cross-tabulated by the following categories of blood alcohol level: number of patients with blood alcohol levels determined, with alcohol in the blood (a "positive" test), and with blood alcohol levels greater than 100 mg per dl. The number of patients with a positive alcohol test, a positive toxicology screen, and both positive blood alcohol and toxicology screen was also tabulated.

The differences in blood alcohol levels between survivors admitted to the ICU and those who lived without being admitted to the ICU were compared with a χ^2 analysis. The χ^2 test was also used to compare the blood alcohol levels of those patients who died and those who survived.

The ISS and total hospital charges of patients with positive and negative blood alcohol tests were compared using the Student's *t* test.

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ABBREVIATIONS USED IN TEXT

ICU = intensive care unit
ISS = Injury Severity Score
UCIMC = University of California, Irvine, Medical Center

Results

Data were available for 2,262 trauma patients (Table 2). Of these, 2,095 (93%) had blood alcohol levels determined. A total of 855 patients (41% of those with their blood alcohol levels measured) had a positive blood alcohol test, and 678 of these (32% of those measured, 79% of positives) had blood alcohol values greater than 100 mg per dl. Of all 2,262 patients, 1,706 (75%) were male. Patients from 16 through 30 years of age accounted for 57% of cases, and the median age was 25 (Figure 2). Of the injuries, 72% were vehicle-related.

The final designation of any trauma patient is subject to base station physician interpretation. Variables for consideration include

- Mechanism of injury
- Age
- Prolonged extrication
- Fatalities involved in the event
- Glasgow Coma Score of 10 or less
- Penetrating wounds of the neck, chest, abdomen, or groin
- Major traumatic injuries resulting in cardiopulmonary distress and/or arrest
- Multiple systems trauma patients with Champion trauma score of 12 or less

Figure 1.—The Orange County (California) revised trauma triage guidelines (instituted February 1983) are used by the Emergency Medical Services for the identification of trauma patients before arrival at a hospital.

Data on the ISS were used only after 1985 because of a change in coding practices, leaving a total of 1,450 patients with data on injury severity. The median ISS was 6 with a range from 0 to 75.

Monthly totals of trauma patients were highest in May and August (Figure 3). The wide variation in monthly totals is partially correlated with the number of weekend days and holidays in each month during the three-year period.

Correlates for Measuring Blood Alcohol Levels

The number of incidents was greatest on Saturday and Sunday (Figure 4). Likewise, the number of patients with positive blood alcohol tests was highest on those two days. By the hour of the day, the total number of incidents increased steadily from 6 AM to 6 PM and remained high until 3 AM. The percentage of patients with positive blood alcohol tests peaked between 2 and 4 AM (Figure 5), with the highest number of intoxicated patients (blood alcohol level higher than 100 mg per dl) in the 2 to 3 AM period.

Having a blood alcohol level measured was significantly associated with the male sex (93.6% of men had a blood

TABLE 1.—*Type of Incident Classification**

Auto/auto	Moped or bicycle
Auto/object	Fall
Motorcycle crash	Altercation
Auto/pedestrian	Industrial†
Gunshot wound	Others‡
Stabbing	

*Does not include drowning, near drowning, or burns.
†Does not include on-the-job motor vehicle-related injuries.
‡Includes many recreational injuries, injury due to falling objects, and the like.

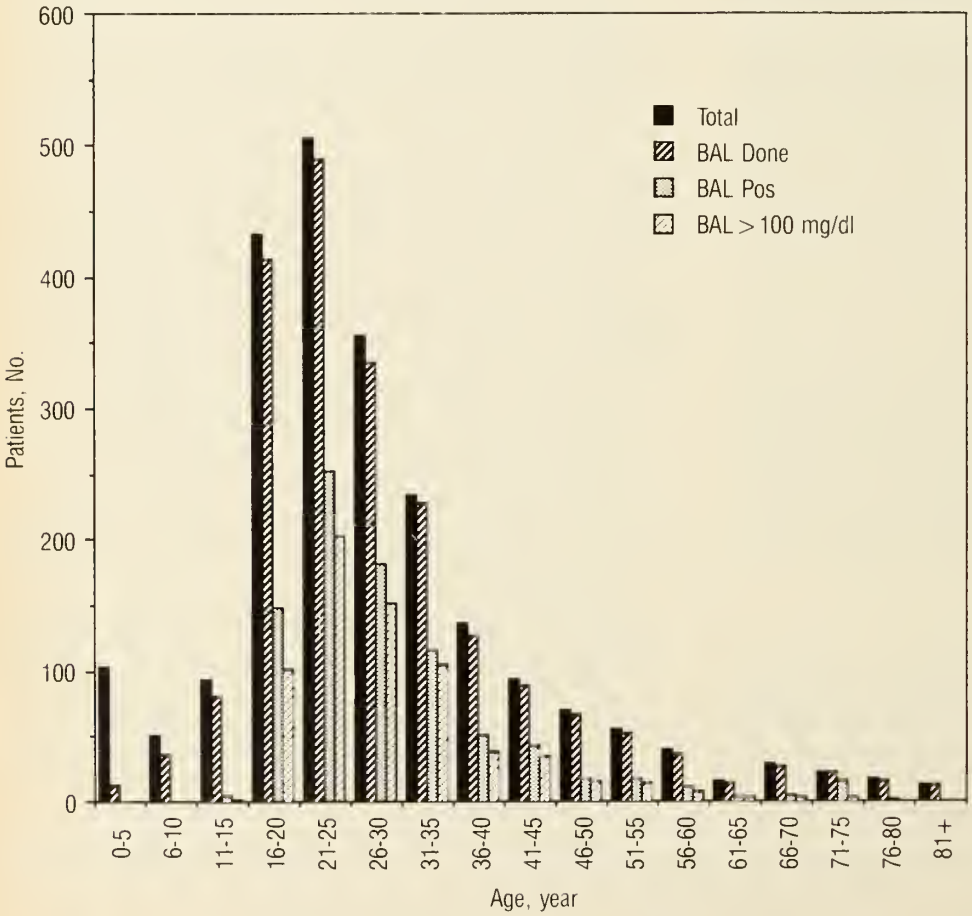

Figure 2.—The bar graph shows age in 5-year increments and blood alcohol levels (BALs) for 2,262 patients. Pos = positive

alcohol level measured versus 89.7% of women, $\chi^2 = 8.87$, $P < .025$) and with an age older than 15 years. Excluding patients 15 years old and younger leaves 2,017 (89%) patients from the original sample; 95.5% of these had a blood alcohol test done, 42.2% of those done were positive, and 33.6% of those levels were higher than 100 mg per dl.

Having a blood alcohol test done also varied by incident type (Figure 6), at least in part because children younger than 15 years old accounted for 36% of pedestrian and 28% of fall injuries. Patients with gunshot wounds may have been less likely to have a blood specimen drawn to test for alcohol because of the severity of injuries.

Although there was no correlation between the blood alcohol level and ISS, a blood alcohol test was not done on more than half (14 of 26) of the patients who were severely injured (ISS of 50 to 75); therefore, further analyses relating blood alcohol levels to ISS were not done because of the potential for considerable bias. Blood alcohol levels tended not to be measured in severely injured patients because of difficulty in obtaining a blood specimen, because of attempts to move patients out of the emergency department as quickly as possible, or because the patient was dead or near death on arrival.

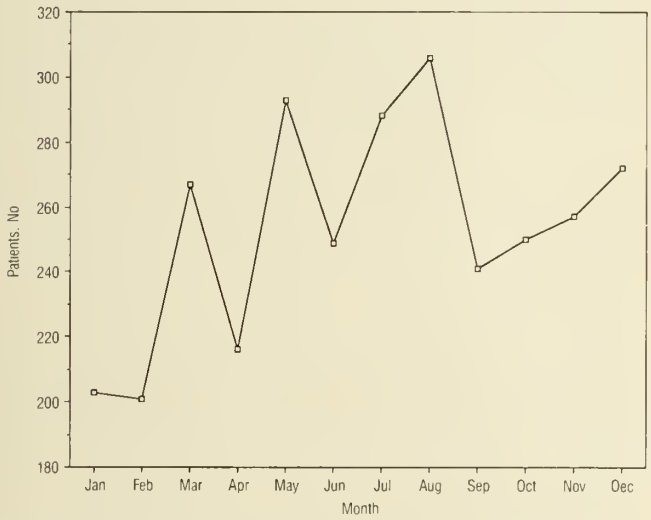

Figure 3.—The chart shows month of injury for 3,043 trauma patients seen at University of California, Irvine, Medical Center trauma center, January 1985 through December 1987.

Correlates of a Positive Blood Alcohol Test

A positive blood alcohol test was associated with age, especially in the 21 to 35 years age group, and with the male sex (46.6% of all men versus 22.4% of all women).

The proportion of patients with a positive blood alcohol test varied with incident type (Figure 6). The highest percentage of patients with a positive blood alcohol test tended to coincide with violent causes of injury (specifically, stabbing at 49% and altercations at 52%) and single-auto crashes (47%). By contrast, for falls, 30% of patients admitted to the trauma center in whom blood alcohol levels were known were intoxicated. In this sample, none of the patients admitted because of an industrial injury showed evidence of alcohol ingestion; however, vehicular causes of industrial injury were not classified as industrial.

Comments

Despite a 93% rate of obtaining blood alcohol levels in 2,262 trauma-designated patients, our data have some limitations. The failure to measure the blood alcohol levels in more than half of the most severely injured patients invalidates any analysis of the relationship between blood alcohol level and severity of injury. Although there is some bias in doing blood alcohol tests, we think we have identified where bias occurs and the reasons for it.

The data available to us did not permit an assessment of interactions among the variables of age, sex, time of day, and incident type, which might have suggested intervention strategies. No attempt was made to assess the blood alcohol levels of a control, noninjured population, but self-reported intake of alcohol appears to be much lower than

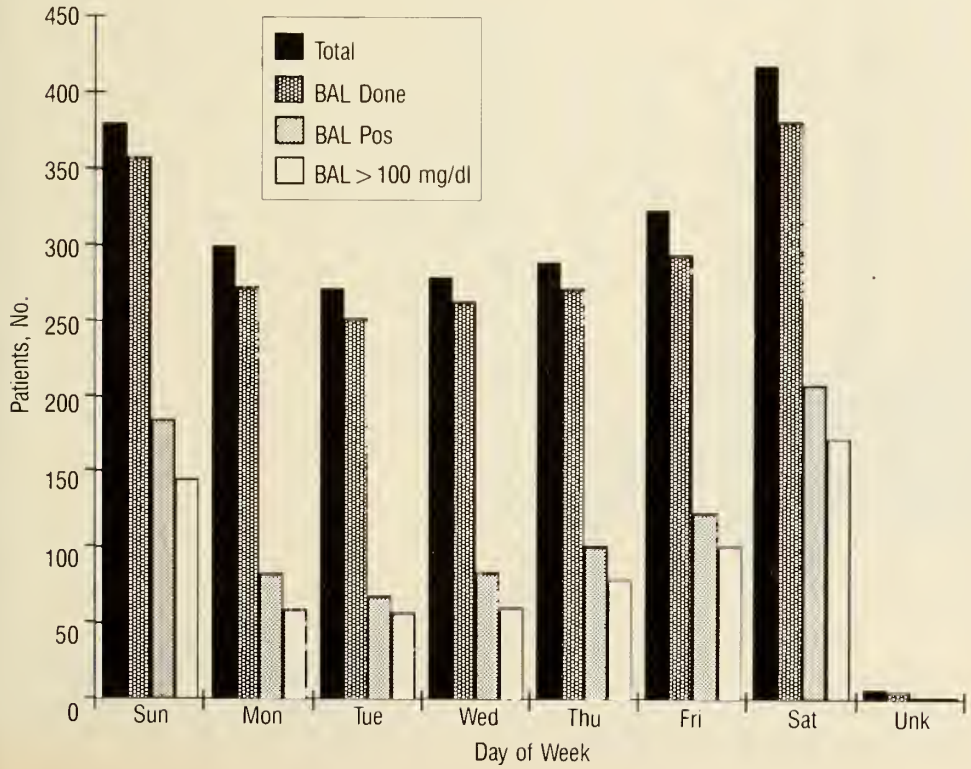

Figure 4.—The bar graph shows the distribution of 2,096 injured patients according to day of the week injury occurred and blood alcohol level (BAL). Pos = positive, Unk = unknown

the 41% positivity found in this series.[14] Information on less severely injured patients is lacking. The blood alcohol levels obtained in the trauma center may, to varying degrees, underestimate or overestimate those at the time of injury because of variations in transport time and the possibility that any given patient's blood alcohol level was rising or falling at the time of injury.

TABLE 2.—*Blood Alcohol Data, Male Sex, and Vehicle-Related Injury Data for 2,262 Trauma Patients*

Variable	Patients No.	Patients %
BAL measured	2,095	93
BAL positive	855	41
BAL greater than 100 mg/dl	678	32
Male	1,706	75
Vehicle-related injury	1,624	72

BAL = blood alcohol level

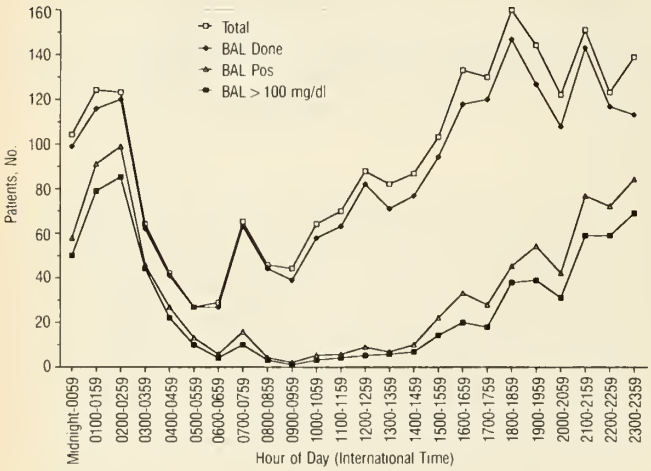

Figure 5.—Hour of day (in international time) and blood alcohol level (BAL) are shown for 2,096 trauma patients seen at University of California, Irvine, Medical Center, January 1985 through July 1987. Pos = positive

Our finding of a 41% rate of positive blood alcohol tests in trauma patients is similar to that found in several other studies. In fact, this similarity is striking in view of the diversity of samples represented—a US Army hospital in Stuttgart,[7] a teaching hospital in Edinburgh,[9] and patients with mild head injuries in a hospital in Belfast[5] all reported similar rates of blood alcohol positivity. Two other studies reported lower (36%)[11] and higher (59%)[8] levels of positivity.

The predominance of men in our series of patients may reflect risk-taking behavior, a greater frequency of alcohol use, a heavier use of alcohol, or, for certain types of trauma, greater risk exposure. Most likely a combination of these factors is involved.

Alcohol use has a pervasive presence in our emergency departments. We think it is important to measure the blood alcohol level in injured patients for several reasons. First, a falsely negative assessment of alcohol use occurs. One study found a false-negative rate of 23% in the clinical assessment of alcohol use in trauma patients (12.5% false-negative rate for patients with a blood alcohol level of greater than 100 mg per dl).[5] Second, a knowledge of the blood alcohol level is important in the diagnosis and treatment of injured patients (because of the possible interaction of alcohol with anesthetic agents, alcohol can both cause an altered state of consciousness and affect the clinical course of a patient with an altered state of consciousness due to other causes) and as a portent of possible withdrawal symptoms in the early treatment period. Finally—and perhaps most important—trauma associated with documented alcohol ingestion signals either a serious alcohol problem or poor judgment in its use.

Clinicians have frequently avoided confronting their patients about habits detrimental to their patients' health, either because the situation is uncomfortable or because of

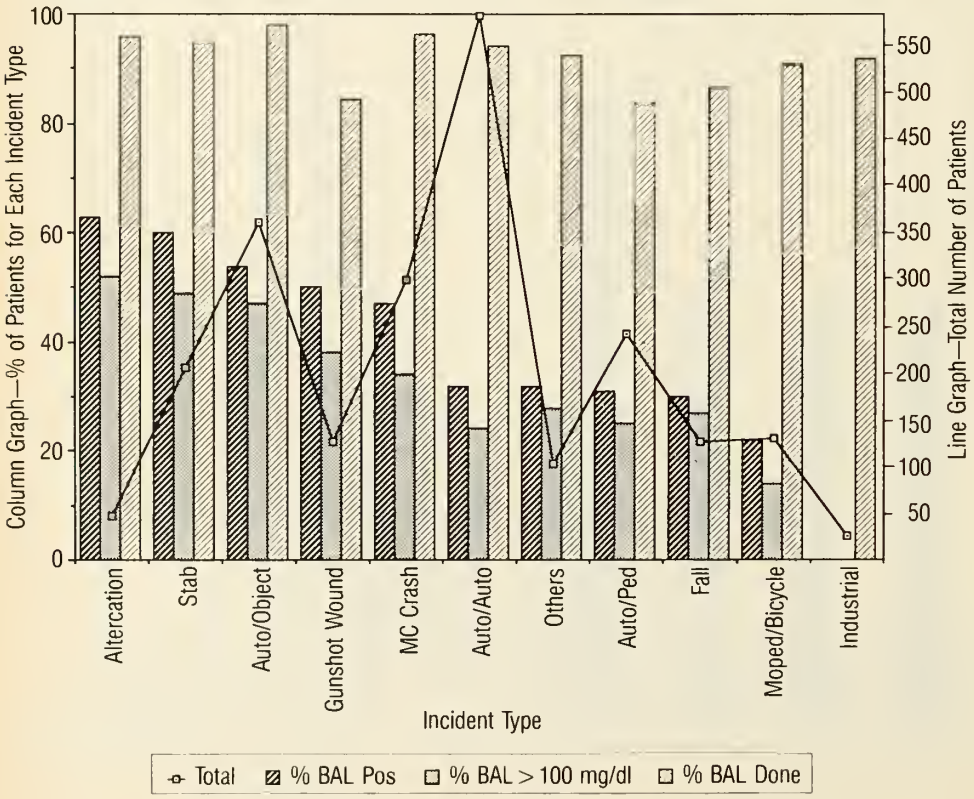

Figure 6.—The incident type and blood alcohol level (BAL) are given for 2,259 patients. The superimposed line graph indicates total number of patients for each incident. MC = motorcycle, Ped = pedestrian, Pos = positive

a perceived lack of confidence in their ability to change deleterious behavior. A survey of trauma centers in 1985 may have reflected this avoidance.[15] In addition, there are concerns about liability and third-party payment when alcohol use is documented; these have not been borne out in the experience of UCIMC.

Changing behavior is notoriously difficult. We cannot predict what experience or thought causes someone to quit smoking, to diet successfully, or to stop drinking alcohol excessively. The aftermath of a serious traumatic injury may prove to be that moment when we have a chance to link a patient's alcohol use with his or her injuries and to trigger a change in behavior. The emergency department is a crucial place for detecting the problem, but detection without a system of appropriate referral and follow-up accomplishes little. At UCIMC, a process for the referral of injured patients with positive blood alcohol tests is being developed.

It is the responsibility of the health care system to treat known risk factors, just as we would treat an elevated cholesterol level. The alcohol-trauma syndrome is an endemic problem with tragic and costly consequences. It should not be overlooked or neglected any longer.

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Articles

From Leningrad to the Day-Care Center
The Ubiquitous *Giardia lamblia*

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Giardiasis is recognized as a worldwide public health problem. Seroprevalence data from both the developing and developed world show high rates of carriage in populations at risk for fecal-oral transmission, such as children in day-care centers. Outbreak investigation has expanded our understanding of reservoirs for *Giardia lamblia* and of the routes of transmission. Various host factors have been associated with infection. The pathogenesis of giardial infections is being elucidated, in particular the role of lectin activation in producing disease. Three standard chemotherapeutic agents are available in the United States. The institution of community-wide prevention measures is equally important. Current areas of investigation including antigenic composition and enzymatic variants should result in effective forms of immunotherapy, while more effective forms of chemoprophylaxis could assist in eradicating the pathogen from institutional settings.

(Shandera WX: From Leningrad to the day-care center—The ubiquitous *Giardia lamblia*. West J Med 1990 Aug; 153:154-159)

A description of the pathogen responsible for giardiasis may be found in the works of Antony van Leeuwenhoek, who discovered in 1681:

> animalcules . . . all of the one and the same make; their bodies [are] somewhat longer than broad and their bellies [are] flatlike, furnished with sundry little paws, wherewith they made such a stir in the clear medium, and among the globules, that you might e'en fancy you saw a pissabed [woodlouse] running up against a wall; and albeit they made a quick motion with their paw, yet for all that they made but small progress.[1]

Such "animalcules," probably *Giardia lamblia*, were not subsequently described until a Bohemian physician, Wilhelm Lambl, ascribed to the organism its first scientific name, *Cercomonas intestinalis*, and elucidated its place in the ecosystem, including it among the fecal flora.[2] Western Europeans recognize his contribution in one of their two names for the pathogen: *Lamblia intestinalis*[3] or *Giardia intestinalis*. The term *Giardia* appears in discussions written by investigators from Berkeley, California, and Germany during the early 20th century; *Giardia* honors a French biologist named Alfred Giard. Hence, the name *Giardia lamblia* honors two 19th-century European scientists.[4,5]

With the modern growth in travel and increased attention to community epidemiology, the importance of *Giardia* species in human disease resurfaced. In the 1960s Americans returning from the Soviet Union with watery diarrhea carried the pathogen in stool; investigations pinpointed the water system in Leningrad.[6] A reported community-wide outbreak wherein *G lamblia* was incriminated occurred in Aspen in 1964-1965: protracted episodes of gastroenteritis developed among those who drank from the city water supply.[7] Such outbreak investigations have supplemented studies of antigenic composition, ultrastructure, life cycle, and enzyme variants in contributing to understanding *G lamblia* and giardiasis.

The Organism and Its Epidemiology

The life cycle of this flagellated protozoan is relatively simple: after cysts are ingested by a mammal, gastric acidity induces excystment and trophozoite development.[8] Trophozoites cause disease, although the mechanism by which disease occurs is debated. Organisms reencyst in the intestine on bile salt exposure[9] and excretion of cysts ensues, although cyst excretion does not have the strict disease dependence of trophozoite excretion, trophozoites being found only in diarrheic stools. The incubation period is usually between 7 and 15 days but may be much longer.[10] The trophozoites are very labile outside the host; cysts survive outside the host if not dehydrated or subjected to extreme temperatures.[11] The estimated infective dose in 50% of the population is between 10 and 100 cysts.[12]

Giardia species infections are ubiquitous. Outbreaks in the developed world have been reported from North America, Europe, and Australia[13-20]; in the developing world, high rates of endemicity have been found in Bangladesh,[21] Nigeria,[22] Guatemala,[23] and Peru.[24] The World Health Organization estimates that about 200 million infections occur annually in the developing world.[25]

In most communities the rate of endemic disease is unknown: giardiasis is often not reportable, variations exist in the methods of collecting specimens, and medical personnel vary in diagnostic skills. In the United States, 4% of stool specimens submitted to state health department laboratories are positive for *Giardia* species.[26] In one jurisdiction with required reporting, the incidence was 17.5 per 100,000 per year; 50% of cases occurred in day-care centers (SW Washington Health District, unpublished data, September 1985).

Community-wide outbreaks are typically from a common source. Although food and body fluids are recognized vehicles of transmission, water is the most common vehicle: the Public Health Service reports that 12 of 99 waterborne outbreaks during a four-year interval were due to *G lamblia*.[27,28] Camping-associated outbreaks are caused by ingesting contaminated water.[11,29] A community swimming pool-associated outbreak may have been due to a toddler soiling in the pool,[30] and a swimming slide-associated outbreak may have developed similarly.[31] Food outbreaks are uncommon; a Minnesota outbreak was associated with ingesting home-canned salmon prepared by an infected handler and served at a rural school[32]; a second in Connecticut was associated with cold noodle salad.[33]

Important community outbreaks include one in Camas, Washington (suburban Portland, Oregon), during 1976 that

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
IFA = indirect fluorescent antibody

affected 128 persons when the surface water supply broke down. Chlorinated and filtered water supplies failed to prevent the outbreak, and water treatment required flocculation, sedimentation, and coagulation.[13] A 1980 outbreak in Red Lodge, Montana, showed how climatic and environmental factors interact in producing disease. After the Mount Saint Helens (Washington) eruption, the deposit of volcanic ash that had been blown eastward, in conjunction with increased snowmelt associated with unusually warm weather, raised the city water supply level; the elevation provided animals access to surface water.[14] Ski resorts have been susceptible to *Giardia* species outbreaks, with reports from both Vail and Aspen, Colorado[7,15]; attack rates in Aspen were associated with the amount of water ingested and the length of residence—longer-term residents in 1981 had lower attack rates, ostensibly because of exposure during a 1964 outbreak.[15] A 1978 New England outbreak revealed the asymptomatic nature of many community-wide infections: 75% of those infected did not require treatment.[16]

Intercontinental travel and migration have been studied in East Germany: foreigners arriving from tropical areas showed higher rates of seroprevalence to *G lamblia* than did German travelers to and from the tropical areas, who had higher rates than German locals.[34] Other studies have outlined the high rates of giardiasis among immigrants from Third World countries.[35]

Well-substantiated methods of transmission also include sexual transmission and person-to-person. Three sexually transmitted disease centers have reported *G lamblia* among the fecal flora of homosexual and bisexual men.[36-38] In a case-control study, 18% of 126 homosexual men carried *Giardia* species, compared with 2% of inpatient and outpatient controls at New York Hospital.[39] Oral-anal sex, however, is not as established a predisposing factor toward giardiasis as it is toward amebiasis and helminthic infections.

Day-care center transmission has been substantiated in the United States, Canada, and Australia[40-45]; age-specific attack rates confirm that childhood disease maintains *Giardia* species in the community. In data from Houston, between 21% and 26% of 600 attendants at 30 day-care centers excreted *Giardia* cysts (trophozoite excretion between 3% and 4%).[40] Case-control methods have revealed that age-matched children not in day-care centers have lower isolation rates than those in day care: 2% versus 29% to 54%.[41] Australian investigators emphasize high rates of asymptomatic infection among children.[42] Family members and household contacts of infected children are at risk, secondary infection rates being between 17% and 47%.[40,42-45]

In summary, the epidemiology of *G lamblia* reveals that transmission occurs by many methods—common sources, sexual transmission, person-to-person nonsexual contact—but water is the usual source of community-wide outbreaks. Environmental factors that may be determinants of outbreaks include the presence of infected animals, the availability of surface water, and climate factors influencing the water supplies. A high prevalence of infection among toddlers and infants is a consequence of fecal-oral transmission in the developed world and water and food exposures in the developing world.

Host Risk Factors

The prevalence of giardiasis, as with any infection, is dependent on host, agent, and environmental factors. Environmental factors have been mentioned; agent factors will be discussed in another section. Host risk factors include sex- and age-specific attack rates. Males are infected more commonly than females [46-51] Age-specific prevalence data show a propensity toward infection in childhood; the prevalence of infection in the younger-than-5 cohort ranges between 4% and 42% (Table 1).[21-23, 46-54] The highest rates occurred in the Nile delta where among 2- to 4-year-old children, 42% showed cyst or trophozoite positivity, with excretion lasting as long as 17 weeks.[54] A difficulty establishing an association between infection and symptomatic illness is a common theme; studies from Peru report frequent reinfections after treatment.[24] Other possible host risk factors include immunodeficiency, human leukocyte antigen phenotype, nutrition status, achlorhydria, blood type, and concomitant infection with other agents, such as *Cryptosporidium* species or *Candida albicans*.

TABLE 1.—*Childhood Prevolence of* Giardia *Species Stool Corrioge*

Population of Endemicity, Age	*Children, No.*	*Stool Specimens Examined, No.*	*Methods*	*Symptomatic, %*	*Prevalence, %*		*Reference Source*
					Childhood	*All Ages*	
Hawaiian school children	390	1	Wet mount	0	4-5	. .	Desowitz and Wiebenga, 1975[46]
Nîmes, France	. .	. .	. .	. .	> 6	. .	Fontaine et al, 1984[47]
Ontario day-care attendees, 2-5 years	244	1	Zinc sulfate	0	6-8	. .	Woo and Paterson, 1986[48]
Washington state infants, 1-3 years	518	1	FEA	. .	7.1*	. .	Harter et al, 1982[49]
Philadelphia inner-city children	385	. .	PVA-FE	. .	8-20	. .	Weiner et al, 1959[50]
Northwestern Australian children, 1-5 years	50	1	PVA-zinc sulfate	32†	12	4	Boreham and Phillips, 1986[51]
Nigerian children in endemic area, 1-5 years	449	1-3	FSE/iodine	. .	13.8	7	Oyerinde et al, 1977[22]
Rural Somalian children and mothers	517	1	Formalin/FE	. .	15-16	. .	Peltola et al, 1988[52]
Guatemalan children, 0-3 years	45	Weekly	PVA/FE/trichrome	0-8.2	20.2	. .	Farthing et al, 1986[23]
Costa Rican children younger than 5 years	293	1	. .	‡	25.3	. .	Moore et al, 1966[53]
Bangladeshi children younger than 5 years	91	. .	Iodine	. .	21-51§	. .	Gilman et al, 1985[21]
Rural Nile delta children, 2-4 years	42	Weekly	Trichrome	. .	42.4‖	17	Sullivan et al, 1988[54]

FE = formalin-ether, FEA = formalin-ethyl acetate, FSE = formol-saline-ether, PVA = polyvinyl alcohol

*21.3% among family member contacts.
†By history.
‡No difference in isolation rate was seen in the presence of diarrhea.
§Seroprevalence is higher among malnourished patients.
‖Cysts and trophozoites.

A variety of immunodeficient states—common, variable; Bruton's; the acquired immunodeficiency syndrome (AIDS)—have been studied with respect to giardiasis.[55,56] Persons with immunodeficiencies may not be at particular risk for severe giardiasis developing.[57-59] X-linked (Bruton's) agammaglobulinemia is not associated with a notable predisposition toward any gastrointestinal illness.[58] A workup for immunodeficiency is not indicated in patients with giardiasis.[60]

HLA phenotypes—A1/A2 and B12/B27—occur with a higher than expected frequency in patients with giardiasis.[61] T-cell deficiencies in animals are not necessarily risk factors; certain strains of mice are more susceptible to *Giardia muris* infections, however, as are congenitally athymic animals.[59] In humans the relationship is less clear. With AIDS, for example, the relationship is complex. A history of giardiasis is associated among homosexual men with an odds ratio of over 10 with the development of seropositivity to the human immunodeficiency virus and AIDS.[62] The incidence of giardiasis among uninfected AIDS patients appears not to be increased, however; homosexual AIDS patients with giardiasis have lower antibody levels than do heterosexual patients with giardiasis—but higher than healthy persons.[63]

Malnutrition is a likely risk factor for giardiasis, although the cause-and-effect relationship between the two is hard to clarify. In Bangladesh 57% of a malnourished cohort aged 1 to 5 was infected with *G lamblia*.[64] A Guatemalan study found, among infected infants, reductions in weight gain (but not height) during the second year of life.[23] A Zimbabwean study also correlated infection with *Giardia* species with indices of malnutrition including wasting and stunted growth.[65] The extent to which immunodeficiency is a significant predisposing cofactor in malnourished patients is unknown.

Persons with blood group A appear to be prone to the recurrence of giardiasis.[66] This is thought to be related to the antigenic similarities between blood group antigens and *Giardia* species: the organism does not evoke the same immunologic reaction it would if the blood group's glycoproteins differed. Data from Finland showed no correlation between blood groups and (nonrecurrent) giardiasis.[67] An association between giardiasis and achlorhydria has also been postulated,[67] although it is essential to control for blood groups because the A blood group is more common among achlorhydric patients.[68] Cystic fibrosis may be a risk factor: a case-control study (using household family members of cystic fibrosis cases as controls) reported higher infection rates among the patients with cystic fibrosis.[69]

In summary, major host risk factors associated with giardiasis are age and perhaps immunodeficiency. Concomitant infectious diseases may reflect acquisition from a common source. Immunotype, blood type, and achlorhydria share a minor role in contributing a propensity toward infection.

Clinical Symptoms

Most giardial infections, particularly those of infancy, are well tolerated and asymptomatic. When overt illness occurs, the spectrum is wide and ranges from an acute, mild, self-limited gastroenteritis to a protracted (the average duration of diarrhea in one Aspen outbreak was 44 days[7]) and debilitated malabsorptive state due to chronic gastroenteritis.[70-75] Frequent symptoms that accompany the gastroenteritis are fatigue, weight loss, abdominal cramps, nausea, and greasy stools.[6] In children malaise, dyspeptic disorders, and a failure to thrive may be due to giardiasis, and in adults symptoms may include a diminished capacity for work.[26] In the developing world, more than 40% of symptomatic infections last between four and six weeks.[23] The relative proportions of symptomatic and asymptomatic infections in areas with high endemicity are unknown (one study in an outbreak setting[16] documented a high rate of asymptomatic infection).

The small intestine, while the most common, is not the only site of disease. Malabsorptive complications associated with giardial infections include vitamin B_{12} deficiency due to nutrient competition,[76] iron deficiency due to impaired absorption,[77] and hypovitaminosis A.[78] Less common, documented complications (typically, case reports) include cholecystitis and mechanical jaundice as well as pancreatitis, upper gastrointestinal bleeding, and mesenteric adenitis.[79-81] Erythema nodosum has been associated with giardiasis,[82] as have ocular inflammation (iridocyclitis, retinal disease),[83] arthritis,[84] and even psychiatric manifestations in childhood.[85] Chronic urticaria is reported to occur with giardiasis and subsides with treatment of the infection; the basis is thought to be mucosal injury with the absorption of toxic materials.[86] Immunoglobulin E levels do not increase in giardiasis.[87]

Pathogenesis

There is no one accepted theory about how *G lamblia* causes disease. Pathologic findings vary but include blunting of small intestinal villi, lymphocytic infiltration, and occasional ulcerations[88-90] and do not correlate well with the disease state.[91] Postulated theories regarding pathogenesis include mechanical obstruction by giardial cysts; mucosal damage by nonmechanical means, toxic or metabolic (a metabolic example is the induction of brush border enzyme deficiencies); and deconjugation of bile salts, either by bacterial overgrowth or by giardial organisms.[59,92] Mucosal invasion is well documented histologically.[93] Indian studies have shown that the size of the inoculum of *Giardia* organisms has no effect, over a twofold log range, on either glucose or amino acid transport in intestinal brush border membrane vesicles of infected mice; hence, mechanical obstruction may not be a primary factor in pathogenesis.[94] In another study, brush border enzyme deficiencies, especially disaccharidase deficiencies, were prominent in a dexamethasone-immunosuppressed mice model.[95] Not all humans show mucosal damage, and enzyme deficiencies may be a consequence rather than a cause of mucosal disturbances. Bacterial overgrowth is also an inconstant finding.[92]

The importance of surface lectins has recently been delineated: *G lamblia* produces a lectin activated by human duodenal secretions (a duodenal protease) and inhibited by trypsin inhibitors. The lectin is inhibited competitively by mannose-6-phosphate and agglutinates to the same site in the duodenum where *G lamblia* attaches. The mechanism of lectin-induced organism attachment and resultant disease is unknown. This system is considered analogous to myxovirus activation by proteolytic cleavage of surface viral glycoproteins or the enhancement of *Trypanosoma cruzi* infections by the proteolysis of its surface membrane proteins.[96]

Serum antibodies against a major 82,000-dalton antigen of *Giardia* trophozoites are present among persons with persistent giardiasis.[97] Substantial indirect fluorescent antibody (IFA) titers have been detected in more than 85% of a Scandinavian adult population, with a fall in titers with treatment.[98] Indirect fluorescent antibody titers were present as long as 18 months in chronically infected persons in a study from Cincinnati; Indochinese refugees and male

homosexuals with AIDS had higher antibody levels than the uninfected.[63] Much of the detected antibody response in populations with high seroprevalence may be due to cross-reaction with other immunogens.[98] High concentrations of anti-*Giardia* antibodies have also been found in the breast milk of mothers in Bangladesh[64]; these antibodies may act in conjunction with free fatty acids of milk because fatty acids are known to be lethal to both *Giardia* cysts and other parasites.[99,100]

Ultrastructural studies have elucidated *Giardia* species motility and attachment.[101-103] The trophozoite attaches to the mucosa with a ventral disc whose ultrastructure consists of multiple microtubules, the outer surface of which contains bridges from which emanate microribbons. Motility is achieved by flagellae whose placement determines the direction of movement: posterior flagellae clear a concave space on the undersurface of the organism for purposes of attachment while caudal flagellae alter the movement of substances within the cytoplasm. Flagellae emerge from axonemes, organelles consisting, like the ventral disc, of microtubules but arranged in a geometrically constant pattern: nine peripheral pairs about two central pairs. Organelles degrade on encystation of the organism. The discovery that chitin is a structural component of cysts[104] suggests a possible therapeutic intervention with chitinases.

Diagnosis

A diagnostic workup includes the collection of several stool specimens—typically three—in polyvinyl alcohol fixative (vials should be given to patients with instructions to take them to a laboratory as soon as possible) followed by the identification of trophozoites or cysts by experienced laboratory personnel.[105] A small bowel biopsy or duodenal aspiration facilitates establishing the diagnosis. Combining stool cultures and duodenal aspiration is especially effective in diagnosis,[106] although the string test (Entero-test; Health Development Corporation) may be preferable. A string embedded in a gel capsule is swallowed, with the proximal end of the string taped to the face; the string is removed three to four hours later, when ostensibly it has reached the terminal duodenum; the distal section should contain bile-stained mucus in which motile trophozoites can be detected.[107,108] An intravenous secretin challenge increases the yield of organisms.[109] A stool enzyme-linked immunosorbent assay is currently available, is 92% to 98% sensitive, nearly 100% specific, and inexpensive; it may eventually replace multiple stool specimens and duodenal aspiration [110] and enable a diagnosis using a minimum of technology in a short interval (less than three hours).[111] Serum IFA levels are commonly present in patients with chronic infection,[63,98] although the correlation between antibody levels and stool specimen positivity in one malnourished cohort was poor.[112] A serum ELISA using cyst antigens has been developed[113] that has high sensitivity (91/92 asymptomatic carriers detected), but specificity is poor (cross-reactivity to heterologous parasitic antigens occurred).

Treatment

Approaches to therapy should consider both the individual and the community: Are individual cases associated with an outbreak? Are physicians receiving current recommendations during an outbreak? It should first be recognized that many infections clear in the absence of treatment.[73,114] The two most popular agents are nitroimidazoles and quinacrine. The nitroimidazoles include metronidazole, tinidazole, ornidazole, and nimorazole (only the first is marketed in the United States). They are effectively given as a single dose (500 mg),[26] although it is generally recommended that metronidazole be given over a seven- to ten-day course at 500 to 750 mg per day in two to three doses.[107,115-122] A major concern with metronidazole use is mutagenicity and carcinogenicity. Its use is usually well tolerated, although patients should be reminded of disulfiram-like effects—which may occur as late as 48 hours after therapy—when taken in conjunction with alcohol. Less commonly reported symptoms include headaches, an unpleasant taste in the mouth, stomatitis, paresthesias, dizziness, and transient neutropenia.[116] Quinacrine is cheaper, but side effects that may limit compliance[119] include gastrointestinal disturbances, blood dyscrasias, urticaria, exfoliative dermatitis, yellowing of the skin, and ocular toxicity; toxic psychoses may occur in 1% to 2% of patients,[123] and hepatic necrosis is rare. Furazolidone is another alternative. A liquid form is well tolerated by children,[124] but gastrointestinal side effects occur, hemolysis may occur in those with a glucose-6-phosphate dehydrogenase deficiency, and it is carcinogenic in animals[119]; the optimal course appears to be ten days.[125] The relative efficacy of the compounds is debatable (none of the agents cure more than 85% of cases), and both metronidazole[26,118,120] and quinacrine[126] have their strong advocates. In an in vitro system using thymidine incorporation, the relative killing efficacy of nitroimidazoles is greater than that of furazolidone, which is greater than that of quinacrine.[127] The World Health Organization currently recommends using nitroimidazoles.[26]

The management of severe cases during pregnancy is problematic; no agent is recommended during early pregnancy. The safety of metronidazole use in children and pregnant women is debatable[107,121]; while some investigators consider it safe to use during pregnancy,[116] in the first trimester its use should be restricted.[117,118] In a recent study of intestinal parasite carriage, including *Giardia* species, among 147 pregnant Thai refugees, there were no complications associated with the parasite infections. The authors consequently advocated withholding all antiparasitic chemotherapy during pregnancy.[128] On delivery, a concern with immediate treatment using metronidazole is its passage into breast milk.[107,129]

Community therapy is directed toward prevention.[13-17] Water sources of *Giardia* species are typically surface water; contaminated water requires either hyperchlorination or the combined methods of coagulation, sedimentation, and flocculation.[13] Filtration alone is insufficient, and chlorination alone requires levels of 2 to 5 mg per liter, levels that make water unpalatable. Boiling cyst-infected water immediately destroys the capacity to excyst.[11] Ozone has potential promise as an inactivating agent.[130] For hikers and campers who use limited quantities of water, iodination is sufficient,[29] although tetraglycine hydroperiodide is safer and easier to use than crystalline iodine.[131]

The proper treatment of institutional outbreaks is controversial.[40,132] It is often recommended that no treatment be given because such infections are usually well tolerated and control measures are hard to execute. Institutional asymptomatic infections, however, may be the source of more insidious or severe infections in the community. Immunoprophylaxis is not available, and chemoprophylaxis will become feasible only with the availability of cheaper, safer medications.

New Areas for Investigations

Topics currently being investigated that should assist in understanding *Giardia* species and its epidemiology include

protozoal enzymes and analyses of zymodenes (the patterns of isoenzyme variation),[133] morphometric observations,[134] animal reservoirs,[26] and antigenic characteristics.[135,136]

Antigenic characteristics assist in the development of serologic assays and immunotherapy.[135] Antigenic variation among organisms is known to occur both in vitro and in vivo, although the biologic significance of such variation is unknown.[135,136] In a recent review of vaccine developments, *G lamblia* was listed among the pathogens for which vaccines are unlikely to be developed in the next decade.[137] Although much work has been produced in the developing world,* there exists a need for epidemiologic studies outlining different modes of spread in the developed versus the developing world.[139] Other epidemiologic and therapeutic studies are needed to refine the role and assess the feasibility of eradicating infection in day-care centers among asymptomatic cyst passers—who are well recognized to maintain the disease.[40-45]

Additional studies on pathogenesis will delineate how lectin activation induces disease,[96] the primary versus the secondary role of brush border enzyme deficiencies,[95] structural-physiologic correlates of the organelles,[101-103] and the role of chitin in the disease.[104] Improved, available diagnostic assays are needed, in particular immunodiagnostic techniques that can establish the diagnosis using either serum or stool specimens.[110,111] Newer forms of chemotherapy are needed as well as assessments of nitroimidazole derivatives,[116,120,121] confirming reported cure rates of more than 90%.[122] The role of the immune system needs to be clarified as well. Further studies delineating the role of the immune system are also needed.

In summary, although *Giardia* species has been a neglected organism with poorly understood pathogenic potential, it is now considered an important cause of gastroenteritis as a consequence of contaminated water and food or venereal exposures. In day-care centers, person-to-person spread is common and asymptomatic cyst passers maintain disease. Periodic major waterborne outbreaks are controlled when attention is directed toward water delivery systems. Current areas for study include parasitic enzymes and antigenic characteristics, relationships to states of impaired immunity, new agents to manage community-acquired (including day-care centers) cases, and ranges of animal reservoirs. The development of safe, effective chemoprophylaxis and immunoprophylaxis should improve the control of giardiasis.

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Articles

Selenium

Nutritional, Toxicologic, and Clinical Aspects

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This is one of a series of articles from western state public health departments.

Despite the recent findings of environmental contamination, selenium toxicosis in humans is exceedingly rare in the United States, with the few known cases resulting from industrial accidents and an episode involving the ingestion of superpotent selenium supplements. Chronic selenosis is essentially unheard of in this country because of the typical diversity of the American diet. Nonetheless, because of the growing public interest in selenium as a dietary supplement and the occurrence of environmental selenium contamination, medical practitioners should be familiar with the nutritional, toxicologic, and clinical aspects of this trace element.

(Fan AM, Kizer KW: Selenium—Nutritional, toxicologic, and clinical aspects. West J Med 1990 Aug; 153:160-167)

Since the recognition of the nutritional essentiality of selenium (Se) in animals in 1957, there has been ever-increasing interest in this trace element. This interest has heightened in the past decade concomitant with the recognition of selenium's essential nutritional role in humans and reports of selenium toxicity among humans. Interest in selenium has been further aroused recently by the findings of elevated levels of this compound in certain soils and water sources in the western United States, leading to adverse effects on fish and wildlife (T. Harris, "Toxic Chemicals Threaten West," *The Sacramento Bee,* September 8, 1985, pp A1, A16-A18, A20).[1,2]

Selenium occurs naturally in various types of soil and can leach into agricultural drain water. This has occurred in the San Joaquin Valley of California, where evaporation pond drain water containing elevated levels of selenium has been associated with adverse reproductive and other effects in aquatic birds at the Kesterson National Wildlife Refuge.[2] Similarly, in California's Salton Sea, Grassland Water District, Tulare Lake Basin, and Suisun Bay, elevated levels of selenium have been found in fish and aquatic birds, necessitating the issuance of health advisories by the California Department of Health Services—that is, recommendations to restrict the consumption of fish and game birds from these areas. Selenium-rich sediments also have been reported in wildlife refuges in Arizona, New Mexico, Utah, Montana, Idaho, and South Dakota (T. Harris, *The Sacramento Bee,* Sep 8, 1985). These findings have caused concern among health and wildlife personnel, as well as the agriculture industry, and have been widely reported in the media, at times causing considerable alarm among the public. Conversely, exaggerated claims about the health benefits of selenium have been made in the popular press. In this article we review the nutritional, toxicologic, and clinical aspects of selenium in an effort to assist physicians with questions and concerns about this compound.

Occurrence

Selenium is a naturally occurring element found in rock, shale, sandstone, limestone, coal, soil, surface water, and vegetation.[3] It occurs in relatively high concentrations in many of the soils of the US, especially the western states, and other parts of the world.[4] Highly seleniferous soils yielding selenium-toxic plants (such as *Astragalus bisulcatus)* are widespread in South Dakota, Wyoming, Montana, North Dakota, Nebraska, Kansas, Colorado, Utah, Arizona, and New Mexico. Soil containing high selenium concentrations but not yielding toxic plants is found in Hawaii.

Chemical Forms

Selenium is a nonmetallic element chemically related to sulfur. It occurs naturally in four oxidation states: elemental selenium, selenite, selenide, and selenate.[3] The valence state affects selenium's toxicity and bioavailability.

Industrial and Commercial Uses

Selenium is used in semiconductor research (aluminum, bismuth, and indium selenide), in the manufacture of glass (ammonium selenite, arsenic hemiselenide), in photoconductors, semiconductors, photoelectric cells, and rectifiers (cadmium selenide), and in electron emitters (calcium selenide); as a catalyst in Kjeldahl digestions (cupric selenide), as a chemical reagent (potassium selenate), in veterinarian remedies for eczemas and fungal infections, and as an antidandruff agent in shampoos for human use (selenium disulfide); in the manufacture of other selenium compounds, and as a reagent for alkaloids (selenium dioxide); and as a veterinary therapeutic agent (sodium selenate, sodium selenite).[5] Radioactive nucleotides of selenium are used as biologic tracers in radiologic diagnostic procedures—selenocysteine Se 75 and selenomethionine Se 75 are used for pancreatic imaging. Selenium is also used as a dietary supplement for some farm animals (sodium selenite), and it is taken as a nutritional supplement by humans (mostly selenium-enriched yeast products). Based on data available to the California Department of Health Services, we estimate that more than 250,000 Californians take selenium as a nutritional supplement.

Environmental Sources of Selenium Exposure

Water

Selenium, in the forms of selenite and selenate, is found in water, principally as a result of leaching from seleniferous rocks and soils.[5] At pH 6.3 to 6.7, precipitation of insoluble

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ferric selenite occurs in the presence of iron. At pH 8, it is oxidized to soluble selenate. The federal and state maximum contaminant level established for selenium in drinking water is 10 parts per billion. Water is generally not a biologically significant source of intake.

Food

The concentration of selenium in plant tissues depends on the concentration and availability of selenium in the soil where the plants are grown. Selenium-accumulator plants grow only in soil containing high levels of selenium—1 to 50 parts per million (ppm)—and accumulate concentrations of as much as 1,000 to 10,000 mg per kg.[5]

Selenium is generally found at levels of less than 1 ppm in food, wet weight. The major dietary sources of human intake are meat, poultry, grain and grain products, and seafood. The dietary selenium intake for the US population has been estimated to be in the range of 60 to 216 μg per adult person per day.[6] A daily intake of 50 to 200 μg of selenium for adults is considered adequate and safe by the Food and Nutrition Board of the National Academy of Sciences.[7] Lower intake levels are recommended for children younger than 7 years.

Air

Most urban areas have atmospheric particulate selenium concentrations ranging from 0.1 to 10 ng per m^3, contributing a biologically insignificant exposure. The occupational threshold limit value for inorganic selenium is 0.2 mg per m^3.[8]

Toxicity

Animals

The toxicity of selenium has been recognized since the 1930s when it was discovered that certain seleniferous soils produced plants having a high selenium content.[3,9] A few species of selenium-accumulator plants characteristically accumulate extremely high levels of selenium in the form of nonprotein selenoamino acids such as Se-methylselenocysteine and can cause acute toxic reactions in animals consuming them. For example, a subacute selenosis called "blind staggers" occurs in livestock feeding on plants containing 100 to 10,000 ppm selenium.[5] This disease is characterized by anorexia, emaciation, neurologic deterioration—blindness, ataxia, and disorientation—and respiratory distress. Generalized paralysis occurs in the final stages of this disease, with death being due to respiratory failure. Likewise, an alkali disease is a chronic form of selenium poisoning among livestock, caused by consuming plants containing 20 to 50 ppm selenium.[5] The major signs of this condition are emaciation and dermatologic changes, such as alopecia and hoof necrosis.[10]

Selenium poisoning has been produced in laboratory animals using various routes of administration.[8,9] Acute toxic exposure causes respiratory distress, pulmonary edema, diarrhea, hemorrhage, and liver and kidney necrosis. Chronic toxic exposure results in gastroenteritis, myocardial injury, pulmonary edema, hydrothorax, renal and liver damage, and, ultimately, death.

The dose of ingested selenium that can cause selenium poisoning depends on the chemical form of selenium, the presence of other dietary components, and the duration of ingesting selenium-rich foodstuffs. In general, chronic selenium poisoning, as manifested by anemia and hepatic necrosis, has occurred in rats and dogs fed diets containing 5 to 15 ppm selenium per day for weeks or months.[8,9] Diets containing 4 to 5 ppm per day have been shown to inhibit the growth of animals, and lower levels can be toxic if the diet is deficient in vitamin E. Similarly, caries formation may be increased if lower levels of selenium are consumed during the development of teeth.

Humans

Toxicity from acute inhalation or dermal contact. Acute human selenium toxicosis has been reported from industrial and other accidental exposures.[10] For example, inhaling selenium fumes, selenium dioxide, or hydrogen selenide causes intense irritation of the mucous membranes of the eyes and upper respiratory tract, producing ophthalmorrhea and ophthalmodynia, coryza, hoarseness, coughing, and sneezing.[7,10] Headache, dizziness, dyspnea, fatigue, nausea, vomiting, a bitter taste in the mouth, and a garlic odor of the breath may also characterize acute inhalational selenosis.

Skin exposure to selenium may cause severe local irritation, producing painful burning, erythema, and occasionally allergic dermatitis. The severity of response depends on the chemical form of the selenium compound. The most severe responses occur after exposure to the highly poisonous hydrogen selenide. Reactions to selenium oxychloride, dioxide, and hexafluoride are less severe. Elemental selenium and selenium sulfides are generally considered nontoxic.

Ingestion. A number of instances of acute selenosis from the ingestion of selenium-containing products or foodstuff have occurred in recent years (Table 1).[12-16] Illustrative of these situations was a case in New Zealand of acute selenosis from ingesting sheep drench containing 22.3 mg Se per kilogram as sodium selenate.[11] In this case, a young girl ingested 1,160 mg of selenium. Her initial serum selenium concentration was 3,100 μg per liter, and the initial 24-hour urine collection showed 680 μg per ml. She had a strong garlic odor to her breath and frequent loose, grey bowel movements. She was treated with gastric lavage, diuresis, and the administration of vitamin C and dimercaprol. She suffered no apparent sequelae, although biochemical tests suggested mild liver damage and electrocardiograms indicated a transient cardiac arrhythmia. She remained well six months after the incident.

A case of ingestion of "coco de mono" nuts in Venezuela containing high amounts of selenium resulted in gastrointestinal disturbances (dyspepsia, diarrhea, anorexia, and a garlic odor of the breath), neurologic symptoms (irritability, nervousness, and minor myalgias), and changes in the hair and nails.[16] The patient recovered completely. In another case, a 3-year-old boy in Australia accidentally consumed a liquid gun-bluing preparation containing 1.8% monohydrated selenium dioxide—H_2SeO_3—which led to bradycardia, slight acrocyanosis, bright red lips, hypersalivation, garlic breath, and death a few hours after ingestion.[17]

An incident occurred in 1983-1984 in the United States during which 13 persons suffered toxic effects from ingesting dietary supplement tablets containing high levels of selenium as the result of a manufacturing error.[12,13] In March 1984, selenium tablets distributed to 39 outlets in 15 states were recalled when an analysis of one lot revealed a selenium content of 27.3 mg per tablet (182 times higher than labeled). Subsequent analyses of tablets from all four implicated distribution lots showed that each tablet contained at least 25 mg of sodium selenite and 4 to 5 mg total of elemental or organic selenium.

Illustrative of the toxicity of these supplements was the case of a 57-year-old woman who had consumed 77 of the 90 tablets from a bottle when she learned of the recall and

consulted her physician. Her tablets were later found to contain 31 mg of total selenium per tablet. The woman noticed pronounced hair loss about 11 days after starting the selenium supplement in late December 1983. This progressed to almost total alopecia over a two-month period. Later, horizontal white streaking on one fingernail, along with tenderness and swelling of the fingertip and a purulent periungual discharge, was noted. These changes subsequently progressed to involve all fingernails. The fingernail from the originally affected finger was eventually lost. She also had periodic episodes of nausea and vomiting, a sour-milk breath odor, and progressive fatigue. Her alopecia was initially attributed to emotional stress consequent to the death of her husband a year earlier. She was treated with oral erythromycin for paronychia after consulting a dermatologist in January 1984. In March 1984, her serum selenium concentration was 528 ng per ml—two to four times the normal level for the US population. Her estimated cumulative dose was 2,387 mg of selenium. This woman was also taking other vitamin supplements, and selenium toxicity was thought to probably have been minimized by the simultaneous ingestion of large doses of vitamin C. Other persons who had consumed the mislabeled superpotent selenium pills had similar symptoms with varying degrees of severity.

Toxicity of Long-term Exposure

Ingesting large amounts of selenium over the long term primarily affects the pulmonary, integumentary, gastrointestinal, and central nervous systems. Symptoms observed in humans suffering from chronic selenium intoxication include depression, lassitude, nervousness, giddiness, emotional lability, dermatitis, gastrointestinal disturbances (primarily nausea and vomiting), a garlic odor of the breath and sweat, excess dental caries, and, in extreme cases, loss of hair and fingernails.[7,14] In all reported cases, symptoms and signs have abated after excess exposure ceases.

There have been no reports of disabling chronic disease or death from industrial exposures,[8] but "rose cold" is a chronic condition occurring in copper workers with exposure to elevated levels of selenium in the ambient environment. The condition is manifested by coryza, cough, and bronchitis, probably due to the production of dimethylselenide, a volatile compound excreted by the lungs and responsible for the characteristic garlic breath of selenium intoxication.

Illustrative of the chronic toxic effects resulting from occupational selenium exposure is the case of a man with a 50-year history of working in selenium refining who died of a myocardial infarction and who at autopsy had red hair and fingernails and numerous noncaseating granulomas in the lungs.[18] High selenium levels were found in the lungs, peribronchial lymph nodes, hair, and nails. The selenium level in the kidney was higher than that in the liver. In fact, there was no accumulation of selenium in the liver, as might be expected from findings in animal models. In humans the target organ of chronic selenosis appears to be the lung, which manifests acute "rose cold" or, as in this patient, a long-term granulomatous hypersensitivity. In contrast, the liver appears to be the target organ of chronic selenosis in test animals.

In areas where alkali disease in cattle has been associated with a high selenium content in soil, water, and vegetation, humans have not been similarly affected. This difference is thought to be due to the difference in human and animal diets, the wide geographic sources of food consumed

TABLE 1.—*Human Health Effects of Dietary Selenium Overexposure*

Reference Source	*Persons Involved, Locotion*	*Form or Source of Selenium*	*Selenium Exposure or Dose*	*Signs, Symptoms, ond Outcome*
FDA, 1984[12] CDC, 1984[13]	12 cases, USA	Superpotent "health food"	Total dose 27-2,387 mg	Nausea, vomiting, nail changes, hair loss, fatigue, and irritability most common; also reported: abdominal cramps, diarrhea, paresthesias, dry hair, garlicky breath
Yang et al, 1983[14]	62-year-old man, China	Sodium selenite tablets	2 mg/tablet/d for 2 yr, equivalent to 1 mg Se/d	Thickened, fragile, honeycomb-like fingernails; gradual recovery after intake stopped
Yang et al, 1983[14]	About 50% of 248 inhabitants in 5 villages, Enshi County, Hubei Province, China	Locally grown plant crops; uptake of Se from soil originating from highly seleniferous coal	Range, 3.2-6 mg/d; average, 5 mg/d; estimated 10 yr after peak prevalence	Most common signs: nail deformation and hair and nail loss; other signs: skin lesions, tooth decay, and neurologic abnormalities Dry and brittle hair easily broke off at scalp, redicles were intact so depigmented and dull hair continued to grow; scalp rash with intolerable itching Brittle nails with white spots and longitudinal streaks on surface; effusion from around the nail New nail had rough and ridged surfaces, was fragile and thickened; broken nail advanced and fell off Skin became red, swollen, blistered, and eruptive; some followed by ulcerations that healed after a long time; primarily on limbs, also on back of neck Mottled teeth, but observation may be confounded by fluoride exposure Neurologic effects seen in one affected village included peripheral anesthesia, acroparesthesia, and dysesthesia Hyperreflexia commonly develped later, followed by numbness and paralysis; one case of hemiplegia
Science News Letter, 1962[15]	North American Indian family, Colorado	Naturally occurring underground water	9,000 μg/liter for 3 mo	Hair loss, weakened nails, listlessness
Kerdel-Vegas, 1964[16]	9 patients, Venezuela	Nuts of the "coco de mono" tree *(Lecythis olloria)* from seleniferous areas	Brazil nuts marketed in the US have been reported to contain selenium at 100 ppm and higher	Most experienced nausea, vomiting, and diarrhea a few h after eating nuts, followed by hair loss and nail changes several wk later; foul breath in 2 patients; a 2-year-old boy died of severe dehydration; gradual hair and nail regrowth and other recovery

COC = Centers for Oisease Control, FDA = US Food and Drug Administration

by humans, and the loss of selenium during food processing.

Two field investigations in 1936 in three seleniferous areas of eastern Wyoming, southern South Dakota, and northern Nebraska suggested mild chronic selenium poisoning among persons consuming locally grown food.[19] Nonspecific symptoms of ill health such as anorexia, indigestion, generalized pallor, carious teeth, a yellowish discoloration of the skin, cutaneous eruptions, chronic arthritis, dystrophic nails, and peripheral edema were observed. A direct causal relationship was not established in either survey, however. There was also no definite correlation between the signs and symptoms seen and the selenium concentration in urine, the highest value being 1.98 μg selenium per milliliter of urine. Likewise, no control group was included in the evaluation. Most of the subjects studied were thought to have a dietary selenium intake of 700 to 7,000 μg a day, assuming an average body weight of 70 kg.

No other suggestive or documented cases of diet-related human selenium intoxication (or deficiency) in the United States have been reported, strongly suggesting that the selenium intake from the typical American diet has been both adequate and safe. The estimated requirements and other comparative dietary intake values for selenium as reported by the World Health Organization[20] are summarized in Table 2.[7,10,14,20-25]

Endemic Intoxication

An endemic chronic selenium intoxication characterized by a loss of hair and nails, skin lesions, and neurologic abnormalities occurred in China in 1961, although it was not reported until 1983.[14] The source of selenium was found to be a stony coal of unusually high selenium content (90,000 ppm), from which the element entered the soil by weathering and thereby became available for crop uptake. The daily dietary intakes of selenium, estimated ten years or more after the peak prevalence had subsided, ranged from 3.20 to 6.69 mg, with an average of 4.99 mg. Hair, blood, and urine selenium levels averaged 32.2 μg per gram, 3.2 μg per ml, and 2.68 μg per ml, respectively. The outbreak was brought on by a drought that caused a failure of the rice crop, forcing the people to consume a restricted diet consisting of locally grown vegetables and maize and few protein foods. The selenium content of corn, rice, and soybeans produced from this area was 500 to 1,000 times tha. of the same crops in an area of China where Keshan disease (selenium deficiency) occurred.

Heart and Motor Neuron Diseases

Although selenium has been touted in the popular press to protect against the development of coronary heart disease, the results of long-term human studies relating serum

TABLE 2.—*Human Dietary Selenium Intakes and the Associated Biologic Significance*

Country or Population	*Dietary Intake Selenium, μg/d*	*Reference Source*
Estimated requirement		
North America		
Men	80*	Levander and Morris, 1984[21]
Women	57*	
New Zealand		
Women	27*	Stewart et al, 1978[22]
China		
Men	9*	Luo et al, 1985[23]
China		
Men, endemic Keshan disease area	7.7†	Yang et al, 1985[24]
Women, endemic Keshan disease area	6.6†	
Men, nonendemic Keshan disease area	19.1†	
Women, nonendemic Keshan disease area	13.3†	
Men	40‡	
Eastern and western populations		
Adults, adequate nutrition	50-60	Combs and Combs, 1986[10]
Estimated toxic, adequate, deficient intakes		
China		
High Se area, selenosis	3,200-6,690	Yang et al, 1983[14]
High Se area, no selenosis	240	
Se adequate area	42	
Low Se area, Keshan disease	3	
Dietary intakes reported		
US		
Population intakes reported	60-216	Ganapathy and Dhanda, 1976[25]
Vegetarian diet	84	
Worldwide nutrition surveys	11-5,000, mostly 20-300	WHO, 1987[20]
Suggested adequate and safe range extrapolated from animal dietary requirement level	50-200	NAS, 1980[7]
Total body content		WHO, 1987[20]
US	14,600 μg	
New Zealand	3,000 to 6,100 μg	

NAS = National Academy of Sciences, WHO = World Health Organization

*Based on metabolic balance studies.
†Based on comparison of dietary intakes.
‡Based on plateau of plasma glutathione peroxidase activity.

selenium levels to the development of coronary heart disease are conflicting.[26]

Shamberger and co-workers concluded that the age-specific death rates for a number of heart diseases were significantly lower in regions of the US with high soil selenium levels than in regions with low selenium levels.[27] An inverse correlation between the plasma selenium level and the severity of coronary atherosclerosis also has been reported.[28] Another study showed no difference in tissue selenium concentrations between patients who died with and those who died without myocardial infarction.[29] In contrast, Salonen claimed that four Finnish studies showed supporting evidence of an increased risk of ischemic heart disease due to low selenium intake as indicated by serum selenium levels of less than 60 μg per liter[30]; three of the original studies referred to by Salonen actually reported little or no association, however.[10]

Three cases of fatal cardiomyopathy have been reported in adult male patients who received long-term (2, 6, and 7 years) total parenteral nutrition (TPN).[31-33] All three patients had low serum selenium levels. Levander discussed the importance of selenium in TPN with regard to the potential for selenium deficiency; he recommended that TPN solutions should be supplemented with selenium to provide 25 to 30 μg Se per day and that blood selenium levels should be monitored.[34]

The reported lower selenium concentrations in toenails and erythrocytes of patients with acute myocardial infarction compared with those of a matched control group were thought to be due to differences in the plant and animal components of the diet rather than the implication of selenium, or its lack thereof, in the causation of the disease.[35,36] Higher levels of selenium may serve as markers for people who eat food derived more from plants (which incorporate selenomethionine) than from animals (which incorporate selenocysteine and inorganic forms of selenium).

Selenium has also been suggested as a possible etiologic environmental factor in an unusual clustering of cases of amyotrophic lateral sclerosis occurring in four farmer-ranchers in west-central South Dakota where chronic selenium intoxication had been noted in farm animals.[10] One patient had elevated levels of selenium in blood and urine. A subsequent investigation of urinary selenium in 20 patients with amyotrophic lateral sclerosis, however, failed to show any relationship.

Teratogenicity

Experimental data on the teratogenicity of selenium have been summarized by Combs and Combs.[10] In brief, malformations were observed in chicken embryos fed a diet supplemented with 8 ppm selenium (as sodium selenite) and in chick embryos treated in ovo with selenium salts. Selenium (as sodium selenite) was not teratogenic when fed to hens at 75 ppm, given parenterally to hamsters at 2 mg per kg body weight, and administered to mice at as much as 1.8 ppm in drinking water. Seleniferous diets from pasturing on seleniferous ranges have, however, been linked to the abnormal development of embryos in pigs, sheep, and cattle.

The teratogenic potential of selenium in humans was suggested by the occurrence of several miscarriages among female laboratory technicians with exposure to selenite powder and the birth of an infant with bilateral clubfoot, but no direct causal relationship between selenium exposure and the untoward events could be established.[37]

Reproductive Effects

In natural seleniferous feedstuff, sodium selenate and sodium selenite can be embryotoxic to chickens and fetotoxic to mice, pigs, and rats.[10] Such feedstuff can reduce the growth rates of chick embryos and of fetal or neonatal mice and pigs. Rats fed seleniferous wheat diets had subnormal growth and reduced reproductive capacity. Pregnant rats given selenium in water at 1.25 and 2.5 ppm had decreased numbers of weaned pups in the second generation. At 7.5 ppm, fertility, number of surviving offspring, and growth rates of the young were reduced. Mice given selenium in drinking water from weaning through several generations had, in the third generation, fewer and smaller litters with more runts. A failure to breed and excessive deaths before weaning were also noted.

Data on semen variables and reproductive performance obtained from 125 men being evaluated for infertility have suggested a role of selenium in reproduction, although the significance of the data remains unclear.[38] A low semen selenium level was associated with a low pregnancy rate, probably resulting from male infertility because artifical insemination with donor semen resulted in pregnancies and normal births; conversely, a high semen selenium concentration was associated with elevated rates of spontaneous abortion and female reproductive failures. The data suggested that a range of semen selenium of 50 to 69 ng per ml was optimal for sperm motility and a low incidence of asthenospermia, and levels of 40 to 70 ng per ml were optimal for overall reproduction—that is, associated with a high pregnancy and low abortion rate.

Genotoxicity

Selenium has shown both antimutagenic and mutagenic properties, depending on the concentration and the chemical form used.[39] The significance of these findings is not clear. In general, sodium selenite is more mutagenic in more mutation test systems than sodium selenate.

Carcinogenicity and Anticarcinogenicity

While selenium has been alleged to be carcinogenic in laboratory animals, deficiencies in experimental design and interpretation of the lesions do not allow for a clear interpretation of the experimental data.[9,20] In particular, neoplastic lesions developed in test animals in some studies only when they had liver cirrhosis produced by overt selenium toxicity. Similarly, tumorigenic effects seen in other studies appeared to be more of a specific effect of the particular compound than of selenium itself. For example, selenium sulfide, an ingredient in certain antidandruff shampoos, has been carcinogenic for rats and female mice when given by gavage, producing hepatocellular carcinomas in male and female rats and female mice and alveolar or bronchiolar carcinomas and adenomas in female mice.[40] But selenium sulfide is a separate and distinct compound, rather than just another salt of selenium; therefore, it cannot be assumed that the results show that other inorganic selenium compounds (selenite or selenate) are carcinogenic.[9]

It also has been suggested that selenium possesses an anticarcinogenic capacity because of findings that it protected against experimental tumor induction in rats and mice, including decreased liver tumorigenesis by *N*-1-methyl-*p*-dimethylaminoazobenzene and decreased mouse skin tumors induced by 7,12-dimethylbenzanthracene.[10,41] The levels of selenium used in these studies were high, however, and nearly produced acute toxicosis in the animals.

Human epidemiologic and demographic studies do not

suggest that selenium is carcinogenic. An inverse correlation has been reported between the incidence of cancer deaths in humans and some regions of the world that are geologically rich in selenium.[42] Blood selenium levels have been reported to be lower in patients suffering from gastrointestinal cancer or liver metastases than in normal patients, although the clinical significance of such findings is unclear. A nested case-control study conducted in northwest Washington during the years 1972 to 1984 suggested that serum levels of selenium had no appreciable effect on the risk of cancer.[43] Nevertheless, the possible use of selenium as an anticarcinogenic agent has evoked experimental and preclinical research.[41,44] A more detailed discussion of the possible carcinogenic and anticarcinogenic effects of selenium is provided by the World Health Organization.[20]

Cataractogenic and Cariogenic Effects

Rats, rabbits, and guinea pigs are susceptible to selenium-induced cataracts following the subcutaneous injection of sodium selenite.[10] This is a peculiar case of selenite acting as a pro-oxidant. A period of particular susceptibility appears to exist 2 to 17 days postpartum.

Exposure to high levels of selenium during the time of tooth development also can increase the incidence of dental caries in animals. Findings from China also suggest a link between above-normal selenium intake and an increased incidence of dental caries.[14]

Interaction With Other Substances

The toxicity of selenium can be altered by interactions with other substances, including sulfate, methionine, cysteine, various heavy metals, arsenic, and vitamins C and E.[9] The function of selenium is intimately related to vitamin E in normal metabolism. It has the capacity to detoxify heavy metals by mutual interaction, but interaction between selenium and other metabolites can either reduce or potentiate selenium toxicity. Selenium can act as an antagonist against various toxic metals, such as arsenic, cadmium, copper, lead, mercury, silver, and zinc.

Nutritional Requirement and Clinical Uses

Animals

Selenium is an essential nutrient for humans and other animals, being required for normal function, growth, and reproduction. The biochemical functions of selenium that are currently recognized include its role as a component of glutathione peroxidase in animals and of several bacterial enzymes.

In animals, selenium deficiency results in stunted growth, liver necrosis, pancreatic atrophy, infertility, and white muscle disease. To be more specific, selenium has been determined to be effective in preventing or ameliorating vitamin E deficiency disorders such as exudative diathesis in chicks and turkey poults; skeletal muscle degeneration and necrosis in chickens, turkeys, ducks, lambs,

TABLE 3.—*Symptomatic Responses in Humans Associated With Selenium Supplementation*

Reference Source	*Patient Population*	*Selenium Status*	*Supplementation*	*Symptoms, Diagnoses, and Responses*
Van Rij et al, 1979[50]	31-yr-old woman	Resided in a rural area of the south island of New Zealand having low Se levels in soil and a history of endemic white muscle disease in sheep Received total parenteral nutrition fluids for intravenous (IV) feeding for 30 d after hospital admission for abdominal exploration and blood transfusion	IV infusion of 100 μg/d Se as selenomethionine	Muscle pain at rest, tenderness to palpation, pain on active and passive movement; muscle tenderness in both legs; no muscle fasciculation or neurologic deficit; returned to full mobility 1 wk after Se supplementation began
Yang et al, 1983[14]	Rural peasants with children younger than 10 yr and women of child-bearing age in Keshan County, Heilongjiang Province, northeastern China	A hypothesis regarding the etiologic role of Se deficiency was proposed because severely endemic areas coincided with areas where incidence of enzootic Se deficiency diseases in farm animals was also high	0.5 mg sodium selenite/wk if 1-5 yr old, 1.0 mg/wk if 6-9 yr old; 4,510 children in trial group, 3,985 in placebo group	Keshan disease; acute or chronic cardiac insufficiency, cardiomegaly, and arrhythmias; ECG changes are criteria for diagnosis; no symptoms or signs specific for identifying the disease Morbidity rate was 1.35% in placebo group, 0.22% in treated group; intervention trials in the following 6 yr resulted in considerably lower incidence in Se-treated children No untoward side effects observed; in some cases, nausea can be overcome by taking the supplement after meals; physical examination and liver function tests showed no adverse effects after 3-4 yr of continuous ingestion of Se
Keshan Disease Research Group, 1979[46,47]	Mostly children	Most endemic areas located in same low-Se zone as the Keshan disease; residents had low blood and hair Se levels, low urinary Se excretion, and low blood glutathione peroxidase activity	Sodium selenite at 1 mg/wk for children aged 3-10 yr and 2 mg/wk for age 11-13 yr; control groups received a placebo; total, 325 Sodium selenite, 0.5 mg/wk for children aged 1-5 yr and 1.0 mg/wk for ages 6-10 yr for 6 yr	Kaschin-Beck disease; chronic, disabling, degenerative osteoarthrosis; 1 year after treatment, x-ray film of metaphyseal changes of fingers showed a decline in the incidence of the disease; in the treated groups, 8.2% of patients showed improvement, 18.1% showed no change, but none were getting worse In the control group, 39.6% showed improvement, 41.5% showed no change, and 30% were getting worse X-ray film showed a decline in incidence from 42% to 4%

ECG = electrocardiogram

calves, and goats; hepatic degeneration in rats, mice, and pigs; testicular degeneration in rats, rabbits, hamsters, dogs, pigs, monkeys, and chickens; failure of gestation in cows and sheep; and growth retardation in immature animals of most species. The daily dietary requirements of various animal species for selenium are in the range of 0.10 to 0.20 ppm (air-dry basis).[10]

Both the amount of selenium required to prevent deficiency symptoms and the amount that will produce toxicity depend on the intake of antioxidants and protein and the presence of other feed and chemicals, the chemical form of selenium, and the age of the animal. In general, selenium in natural feedstuff is less toxic than similar exposures to selenium in water or purified feed. Dietary exposure is less toxic than parenteral or inhalation exposure. The intake of mineral and rough or high-protein feed reduces toxicity. It is important to remember that selenium's margin of safety is relatively narrow.

Humans

In patients receiving long-term parenteral alimentation, selenium deficiency may become clinically important.[31-34,45] Similarly, beneficial responses to selenium supplementation, as described later, have been observed in persons living in low-selenium areas of New Zealand and China.[45-49] The symptomatic responses seen following selenium supplementation are presented in Table 3.[14,46,47,50]

A selenium-responsive condition known as Keshan disease poses an important health hazard to peasants in China.[40,41] This is a type of cardiomyopathy most often affecting children younger than 15 years and women of childbearing age in the northern provinces and children 2 to 7 years of age in southern China. Its occurrence has been invariably associated with a low hair selenium content (generally < 0.12 μg per gram in affected areas, 0.12 to 0.2 μg per gram in unaffected areas near the affected region, and 0.25 to 0.6 μg per gram in areas removed from the affected region). Affected populations have been known to be in a selenium-poor state by urinary selenium loading tests and whole blood glutathione peroxidase activity measurements. The blood selenium concentrations of persons living in the affected areas often are less than 0.01 μg per ml, while the lowest value in unaffected areas was about 0.04 μg per liter. Clinical trials using supplemental sodium selenite showed that taking the compound was effective in reducing morbidity from the disease. Selenium administration did not cause side effects in children. Physical examination and liver function tests revealed no hepatic damage after continuous selenium administration for three to four years. Selenium deficiency accounted for most of the features of the disease, but the absence of a correlation between the seasonal prevalence of Keshan disease and the variations in hair selenium content suggest that factors other than selenium may be involved.

Selenium supplementation may also be effective in reducing the incidence and severity of Kaschin-Beck disease, an osteoarthropathy endemic to eastern Siberia, northern Korea, and parts of China.[46-48] The endemic distribution of the disease in China is similar, but not identical, to that of Keshan disease—that is, both are prevalent only in the long belt of selenium deficiency in that country.

Kaschin-Beck disease primarily affects the epiphyseal and articular cartilage and epiphyseal growth plates of growing bones. Affected cartilage shows atrophy and necrosis with repair and disturbance of endochondral ossification. The most striking feature is chondronecrosis, with proliferation of surviving chondrocytes in clusters. The condition results in enlarged joints, especially of the fingers, toes, and knees; shortened fingers, toes, and extremities; and, in severe cases, dwarfism. The characteristic enlargement of joints in patients with Kaschin-Beck disease gives rise to the name "big bone joint" disease. This disease is most prevalent among children aged 6 to 15 years but has been diagnosed as early as 13 weeks of age. It occurs more frequently in the winter and spring months. Supplemental selenium (oral sodium selenite, 0.5 to 2 mg per week) combined with vitamin E was therapeutic in 83% of patients with radiographically diagnosed disease.[46,47] Another study showed that administering sodium selenite tablets, 1 to 2 mg per week, was effective in reducing the severity and facilitating the resolution of the disease, whereas selenized table salt (20 ppm selenium) was ineffective.[49] In sum, while selenium deficiency appears to play an important role in the origin of Kaschin-Beck disease, it cannot be considered solely a selenium deficiency disorder. It is, instead, a selenium-responsive condition.

Current Trend in Dietary Supplementation

While the possible use of selenium in cancer prevention and chemotherapy has been suggested[41,43,44,51] and is the focus of clinical research, dietary selenium supplementation has also become a popular health fad, with claims being made in the popular press for the prevention of angina, arthritis, cancer, cerebrovascular disease, aging, infections, cataracts, periodontal disease, kwashiorkor, and the sudden infant death syndrome.[10,17,52] Currently, there are, however, no or insufficient data to recommend selenium supplementation as a prophylactic measure for any of these conditions, and there is reason to be concerned about overzealous selenium supplementation. Thus, at present, selenium dietary supplementation cannot be recommended on a routine basis.

Metabolism

Selenium compounds are easily absorbed from the intestinal tract.[20] In studies of rats, 95% of ^{75}Se administered by stomach tube was absorbed. Similarly, high absorption was reported in women given selenomethionine or selenite in water. The adult body burden of selenium ranges from 3 mg (New Zealand) to 14.6 mg (United States). The kidney and liver normally contain higher levels of selenium than other tissues, and muscle contains the highest proportion of the total body selenium.

Selenium is thought to be incorporated into the tissue proteins as the amino acid selenomethionine. Excretion following oral tracer doses of inorganic or organic selenium compounds in humans is mainly by the urinary tract, but naturally occurring selenium in foods is excreted equally by the urinary and intestinal tracts. High exposure also results in substantial respiratory excretion of volatile selenium compounds in animals. Whole body counting studies using single doses of ^{75}Se-labeled compounds showed an initial phase of a rapid decrease of whole body radioactivity for several days, followed by a more gradual phase of excretion. Data from studies of animals indicated that both phases of excretion were affected by the antecedent whole body burden of selenium, but the initial phase was also affected by the dose administered.

Diagnosis and Treatment of Selenium Toxicity

As previously discussed, acute selenium overexposure in humans is associated with nausea and, in some cases, vomiting and diarrhea. Acute and chronic selenosis produces nail and hair changes, peripheral neuropathy, fatigue, and irritability. A garlic odor of the breath also has been de-

scribed, although this is characteristic of several other poisons as well.

Specimens of whole blood, serum, or plasma are commonly used to measure human selenium exposure. Whole blood is thought to provide a better measure of long-term exposure. The blood selenium content, however, can be affected by the vitamin E content of the diet; exposure to inorganic mercury, cadmium, or other dietary or environmental factors; and whether the form of selenium is selenomethionine, selenate, or selenite. Urinary levels can be useful for assessing recent selenium exposure—within the past 24 hours—but must be interpreted with caution. Hair selenium content has been measured in animals, and in situations where external contamination can be positively excluded, it may be useful for assessing the selenium status in humans.

No completely satisfactory treatment of selenium toxicity is available.[53] The treatment of selenium poisoning suggested in most references has been inadequate or even misleading.[11,17] Nonspecific supportive measures that have been suggested for acute toxic ingestions include gastric lavage, respiratory assistance as needed to maintain adequate oxygenation, and the intravenous administration of fluids and vasopressors for circulatory support.[11] These general measures may be effective in cases involving a marginal lethal dosage, but they are not likely to be adequate in patients with profound overdosage.

Specific treatment with *p*-bromobenzene has been beneficial in some cases, although the hepatotoxicity of this compound effectively precludes its use in humans.[10] Another specific therapeutic intervention that has been recommended is the use of a reductant-containing bathing solution or ointment, such as 10% sodium thiosulphate, to prevent pain and necrosis in cases of burns due to a topical exposure to selenium trioxide or hydrogen selenide.[10]

Conclusion

Selenium is an essential nutrient at low levels of intake and a toxicant at high intake levels for both humans and animals. Selenium-induced toxicosis is exceedingly rare in the United States, however. Unusual cases of acute selenosis have been reported from industrial accidents, but chronic selenosis is essentially unheard of in this country because of the typical diversity of the American diet. Nonetheless, clinicians should be familiar with the possible toxicity of selenium, as well as its possible benefits, because of growing public use of this compound as a dietary supplement and because of concerns raised by the occurrence of environmental selenium contamination and resultant wildlife toxicity in several areas of the western United States.

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Conferences and Reviews

Prostaglandins, the Kidney, and Hypertension

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Prostaglandins are part of the family of oxygenated metabolites of arachidonic acid known collectively as eicosanoids. While they are formed, act, and are inactivated locally and rarely circulate in plasma, they can affect blood flow in some tissues and so might contribute to the control of peripheral vascular resistance. Few studies have shown any derangement of total body prostaglandin synthesis or metabolism in hypertension, but increased renal synthesis of one prostanoid, thromboxane A_2, has been noted in spontaneously hypertensive rats and some hypertensive humans. This potent vasoconstrictor may account for the increased renal vascular resistance and suppressed plasma renin activity seen in many patients with hypertension. Increased renal vascular resistance could increase the blood pressure directly as a component of total peripheral resistance or indirectly by increasing glomerular filtration fraction and tubular sodium reabsorption. Specific thromboxane synthesis inhibitors not only decrease renal thromboxane production but also increase renal vasodilator prostaglandin synthesis when prostaglandin synthesis is stimulated. This redirection of renal prostaglandin synthesis toward prostacyclin might be of benefit in correcting a fundamental renal defect in patients with hypertension.

(Wilson TW, Kaushal RD, Dubois M: Prostaglandins, the kidney, and hypertension. West J Med 1990 Aug; 153:168-172)

It is now more than half a century since the smooth muscle-contracting effects of lipids extracted from seminal fluid were discovered and more than three decades since the structures of the prostaglandins were elucidated. Given their potent vasoactive effects, it is hardly surprising that prostaglandins have been implicated in the pathogenesis of hypertension. In this review we briefly discuss the prostaglandins and their effects on the kidney, then advance a hypothesis that a specific aberration in renal prostaglandin synthesis, namely an overproduction of thromboxane A_2, might lead to the process of hypertension.

Eicosanoid Synthesis and Metabolism—An Overview

The prostaglandins (PG), thromboxanes (TX), and lipoxygenase and epoxygenase products are collectively called eicosanoids. They are oxygenated derivatives of a number of long-chain (20-carbon) polyunsaturated fatty acids including dihomo-γ-linolenate (C20:3, ω6), arachidonate (C20:4, ω6) and eicosapentaenoate (C20:5, ω3). These polyunsaturated fatty acids can be synthesized from essential fatty acids by some species like the rat but in most, including cats and humans, must be taken in the diet.[1] The current North American diet ensures that arachidonate is most prevalent. Once absorbed, polyunsaturated fatty acids are incorporated into cell membrane phospholipids in virtually all tissues. This efficient acylation is presumably responsible for the low concentrations of arachidonate found in plasma and intracellular water.[2]

Several tissue- or organ-specific stimuli cause a transient increase in cytosolic arachidonate by activating phospholipase A_2 or other phospholipases (Figure 1). They include hormones like angiotensin II, neurotransmitters like norepinephrine, and even the mechanical disruption of cells. After its release, arachidonate (or other polyunsaturated fatty acids) can be oxygenated by one of three enzyme systems. Cyclooxygenase forms an endoperoxide, PGG_2; lipoxygenases form hydroxyeicosatetraenoic acids and leukotrienes, and cytochrome P-450 epoxygenases form epoxides. Prostaglandin G_2, in turn, is metabolized by tissue-specific enzymes to prostacyclin (PGI_2), thromboxane A_2 (TXA_2), PGE_2, PGD_2, and $PGF_{2\alpha}$. In endothelia, PGI_2 is predominant, but if its synthesis is decreased, the others, including TXA_2, can be produced nonenzymatically and assume relatively greater importance.[3] This situation is seen in endothelial cells harvested from older animals where PGI_2 synthesis is decreased, possibly because of an increased amount of lipid peroxides, which inhibit PGI_2 synthase.[4]

It is possible that endoperoxide synthesized in one cell type, such as platelets, can be further metabolized by another, such as endothelium.[5] In in vitro experiments, platelet-derived endoperoxide was shown to be metabolized to prostacyclin by aspirinated endothelial cells. Because aspirin inhibits cyclooxygenase irreversibly, the endothelium must have used PGG_2 from platelets.

The mechanism of control of the enzymes necessary for prostaglandin synthesis has been extensively investigated and recently reviewed.[6,7] The initial, rate-limiting step, release of arachidonic acid, is mediated by phospholipases and diglyceride lipase in or near the cell membrane. The stimuli mentioned earlier activate phospholipases. The enzyme or enzymes catalyzing the reverse reaction, reacylation of arachidonate, have received less attention. It is of interest that both groups of enzymes are activated by an increase in intracellular calcium.

Cyclooxygenase appears to be localized in or near the rough endoplasmic reticulum. It can be inactivated when its product, PGG_2, is reduced to PGH_2, yielding a highly reactive singlet oxygen. This appears to be a mechanism to limit prostaglandin and thromboxane synthesis. Prostaglandin H_2 can be metabolized to PGE_2, PGD_2, or $PGF_{2\alpha}$ by specific isomerases. Reduced glutathione appears to increase the synthesis of PGE_2 by activating its isomerase. Thromboxane synthase is a cytosolic, P-450-type hemoprotein. Prostacyclin synthase is located in or near the plasma membrane and nuclear membrane. It is readily inhibited by

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This work was supported in part by grants in aid from the Saskatchewan Heart Foundation and the Upjohn Company of Canada.
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ABBREVIATIONS USED IN TEXT

PG = prostaglandin
TX = thromboxane

many lipid hydroperoxides, an effect that is reversed by free radical scavengers.

Lipoxygenases and microsomal epoxygenases are present in some cells, including some in the kidney. Because much less is known about the function of their products, they will not be considered in detail. Their overall contribution to renal function appears to be small because indomethacin, a cyclooxygenase inhibitor, can block all measurable effects of arachidonate infused into the renal artery.[8] On the other hand, stimulating epoxygenases with stannous chloride in young spontaneously hypertensive rats can prevent the development of hypertension.[9] No antihypertensive effect occurs in adult animals with established hypertension.

Certain drugs can inhibit the activity of phospholipase, cyclooxygenase, prostacyclin synthase, or thromboxane synthase.[6] Cyclooxygenase is inhibited irreversibly by aspirin and reversibly by nonsteroidal anti-inflammatory drugs like indomethacin.

Prostaglandins and thromboxane can be exported out of their cell of synthesis and affect nearby cells. Because of efficient inactivating mechanisms, however, they are rarely found in circulating blood.[10] Among the inactivating factors are dilution in areas of high blood flow, spontaneous hydrolysis (TXA_2 to TXB_2, half-life 30 seconds; PGI_2 to 6-keto-$PGF_{1\alpha}$, half-life 3 minutes), and a number of enzymatic conversions. For each of the prostaglandins and TXA_2, it has been possible to identify a major metabolite whose urinary excretion rate provides an estimate of the total body synthesis of the parent compound.

Actions of Eicosanoids

The diverse pharmacologic actions of the eicosanoids can be classified as those affecting platelet-mediated hemostasis, those affecting blood flow or smooth muscle function, those affecting the release or action of other effector systems, and those affecting cell integrity (cytoprotective effects). Different eicosanoids often can have opposite biologic effects. For example, TXA_2 is a potent vasoconstrictor

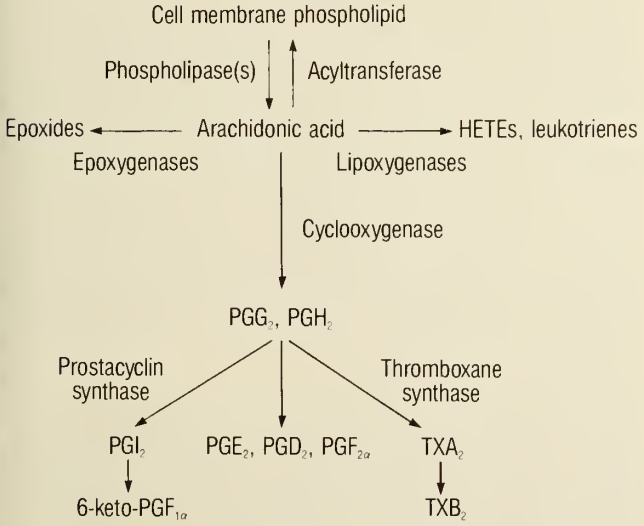

Figure 1.—The diagram shows the arachidonic acid cascade. HETEs = hydroxyeicosatetraenoic acids, PG = prostaglandin, TX = thromboxane

and aggregates platelets, and PGI_2 is a vasodilator and prevents platelet aggregation.[12]

Distinct cell membrane receptors for TXA_2, PGI_2, PGE_2, PGD_2, and $PGF_{2\alpha}$ have been partially characterized.[13] Other eicosanoids bind to and stimulate these receptors to varying degrees. For example, PGH_2, an endoperoxide, is a thromboxane receptor agonist, while PGE_1 can stimulate prostacyclin receptors. In some cases postreceptor events have been characterized. Activation of the platelet thromboxane receptor causes phospholipase C activation, increased intracellular inositol triphosphate, increased intracellular calcium, and a secondary inhibition of adenylate cyclase.[13] Prostacyclin increases the activity of adenylate cyclase and adenosine 3′:5′-cyclic phosphate (cyclic AMP), which leads to a decrease in the amount of intracellular calcium.[13]

Eicosanoids and Kidney Function

The renal cortex and medulla contain all the components of the eicosanoid system: precursor polyunsaturated fatty acids, synthetic and degradative enzymes, and receptors.[14,15] There appears to be some compartmentalization of synthesis so that afferent arterioles produce mainly PGI_2 (presumably from endothelial cells), glomeruli PGE_2 and TXA_2, and interstitial cells and collecting ducts, mainly PGE_2. This rigid separation may not be absolute, as the detection of eicosanoid synthesis by isolated cells or tissues depends on the sensitivity of the measurement, whether or not substrate (arachidonate) is added, and the presence of cofactors or inhibitors. In addition, cells in culture change in their ability to synthesize eicosanoids and the mix of eicosanoids produced as the number of generations in culture increases.

Effects on Renal Blood Flow

When arachidonic acid is infused into a renal artery of most species, renal vasodilation results.[16] Administering indomethacin abolishes this response, suggesting that a cyclooxygenase product is responsible. A rat kidney responds to high rates of arachidonate infusion with a vasoconstriction that is again blocked by the use of indomethacin.[17] This is consistent with the action of a vasoconstrictor cyclooxygenase metabolite, such as thromboxane A_2. Administering captopril, an angiotensin-converting enzyme inhibitor, partially reverses the vasoconstriction, suggesting that PGI_2-mediated renin release (to be discussed later) might contribute to it.

Inhibiting renal cyclooxygenase by adding aspirin or nonsteroidal anti-inflammatory drugs, such as indomethacin, has widely varying effects. The elegant experiments of Terragno and co-workers showed that giving indomethacin, even in high doses of 10 mg per kg, has little effect on the renal blood flow in conscious dogs but reduces the flow by 40% in anesthetized and laparotomized dogs.[18] Furthermore, a surgical procedure and anesthesia increased the plasma renin activity and the amount of renal vein PGE. Other investigators have shown that hemorrhage, sodium restriction, or direct angiotensin II infusion cause greater vasoconstriction in indomethacin-treated animals. There are several case reports documenting acute, reversible declines in the glomerular filtration rate in patients suffering from the nephrotic syndrome or congestive heart failure who receive indomethacin.[19] Thus, when a kidney undergoes vasoconstrictor stress, prostaglandin synthesis is increased to help maintain the renal blood flow and glomerular filtration rate. When prostaglandin synthesis is inhibited, the renal blood flow and glomerular filtration rate can decrease dramatically. It should be noted that renal

autoregulation during milder changes in the renal perfusion pressure is not dependent on eicosanoid synthesis.[20]

The possibility that eicosanoids can act as renal vasoconstrictors was first suggested by Morrison and associates.[21] They found that a ureter-obstructed rabbit kidney produced TXA_2 in contrast to its unobstructed counterpart. Later studies showed that the increased TXA_2 synthesis correlated with an infiltration of the damaged kidneys with mononuclear cells.[22] It is also clear, however, that a normal kidney can produce TXA_2 and that TXA_2 can contribute to renal vascular resistance (to be discussed later).

The transient renal vasodilation seen with the use of furosemide and other high-ceiling diuretics is prostaglandin-dependent, probably due to PGI_2. Furosemide given intravenously increases the availability of arachidonic acid to cyclooxygenase, presumably by stimulating a phospholipase.[23] The resulting production of PGI_2 is reflected by the increased excretion of its hydrolysis product, 6-keto-$PGF_{1\alpha}$, and decreased renal vascular resistance.[24] Oral furosemide[25] or lower doses given intravenously[24] produce natriuresis but do not increase eicosanoid excretion or renal blood blow.

Effects on Renin Release

The relationship between the renin angiotensin system and renal eicosanoids is complex. As stated earlier, angiotensin II is a major stimulus to renal eicosanoid synthesis. It is also clear that renal eicosanoids can affect renin release. Although there are formidable methodologic problems,[26] it is generally agreed that prostaglandin synthesis, again, particularly PGI_2, contributes in large measure to two of the three endogenous mechanisms of renin release: the baroreceptor and the macula densa. A third mechanism, β-adrenergic stimulation, seems to be independent of prostaglandin synthesis.[27] To our knowledge, there has been no direct documentation of the effect of TXA_2 on renin release, but given its ability to increase intracellular calcium[13] and the inhibition by calcium of renin release,[28] it seems plausible that an inhibiting effect of TXA_2 might exist. Such a mechanism would provide a dampening of a positive feedback loop whereby angiotensin II stimulates PGI_2 synthesis, which in turn causes renin release. If angiotensin II also increased the synthesis of TXA_2, the negative feedback circuit would be closed.

Effects on Sodium Excretion

No area of eicosanoid research is more controversial than their effects on sodium excretion. Eicosanoids have been reported to increase, have no effect on, or even decrease sodium and water excretion. Among the more generally accepted concepts are that nonsteroidal anti-inflammatory drugs cause modest sodium retention[29] and that pressure natriuresis is at least partially dependent on increased renal medullary PGE_2 synthesis.[30] Furthermore, a permissive effect of prostaglandin production on sodium excretion in response to volume loading is seen only under conditions of sodium depletion.[31] In summary, renal prostaglandins appear to have little effect on sodium balance at the usual dietary intakes and in the absence of vasoconstrictors. In the presence of a vasoconstrictor stress, however, prostaglandin synthesis or the mixture of eicosanoids produced may affect sodium excretion (to be discussed later).

Total Body Synthesis of Eicosanoids in Hypertension

Measurements of Eicosanoids and Their Metabolites

Given that increased peripheral vascular resistance is characteristic of most forms of human and experimentally induced hypertension, an attractive hypothesis is that there may be an imbalance of vasodilator and vasoconstrictor eicosanoids. Early studies done with vascular rings studied in vitro, however, showed increased PGI_2 synthesis in hypertensive animals.[32] Furthermore, PGI_2 synthesis decreased toward normal in vessels protected from hypertension by a vascular clip, suggesting that the increased PGI_2 synthesis was a nonspecific reaction to hypertension.[33] The relevance of the production of PGI_2 by large conducting vessels to the control of peripheral resistance by resistance vessels is questionable. Also, it may not be possible to correlate in vitro production from a single vascular site with total body synthesis. More recently it has become possible to estimate total body PGI_2 and TXA_2 synthesis in vivo by measuring excretion rates of their most abundant urinary metabolites, 2,3-dinor 6-keto-$PGF_{1\alpha}$ and 2,3-dinor TXB_2, respectively.[34,35]

Falardeau, Martineau, and colleagues found that a high-salt diet caused an increase in the total body synthesis of PGI_2 in rats resistant to salt-induced hypertension.[36,37] Salt-sensitive rats failed to show this compensatory increase. Preliminary data in hypertensive humans also suggest a relative decrease in total body PGI_2 synthesis with increasing blood pressure, but TXA_2 synthesis remains unchanged.[38] Although it is tempting to ascribe an increased total peripheral resistance to a decreased ratio of vasodilator (PGI_2) to vasoconstrictor (TXA_2) eicosanoid synthesis, there are several pitfalls. First, the proportion of PGI_2 excreted as 2,3-dinor 6-keto-$PGF_{1\alpha}$ is small—about 5% to 10%[39]—so that minor changes in the rate of metabolism could produce substantial errors in estimating the rate of synthesis of the parent compound. Second, much of the total body PGI_2 synthesis takes place in large conducting arteries. In patients with severe atherosclerosis, excretion of 2,3-dinor 6-keto-$PGF_{1\alpha}$ is elevated twofold to tenfold,[40] presumably due to an increased synthesis by large vessel endothelial cells in response to platelet activation caused by atherosclerosis. These patients had blood pressure readings that were not different from controls. Taken together, these data suggest that the commonest cause of elevated total body synthesis of PGI_2 and TXA_2 is increased platelet activation due to large vessel damage. It remains possible that increased PGI_2 synthesis in conducting vessels and TXA_2 in platelets can affect downstream resistance vessels, but the effect is likely to be small.

Inhibition of Eicosanoid Synthesis

If resistance vessel tone were dependent on vasodilator eicosanoid synthesis, inhibitors of cyclooxygenase might be expected to increase the peripheral vascular resistance and blood pressures. Short-term studies with indomethacin, 150 mg given daily for a week, produced no change in blood pressures in normal volunteers,[41] but in longer term studies the blood pressures increased slightly.[42] Similar modest effects on the blood pressure have been shown in patients with hypertension.[43] It is possible that a decreased cardiac output could mask any hypertensive effects of an increased peripheral resistance, but in most studies sodium retention was noted, which would be expected to increase or at least maintain the cardiac output.

Stimulation of Eicosanoid Synthesis

The intravenous administration of arachidonic acid is lethal in many species because of intravascular platelet aggregation. In dogs arachidonate produces vasodilation without platelet activation.[16] Supplementing the diet with the arachidonic acid precursor, linoleic acid, produces a small decrease in blood pressure in humans with hyperten-

sion, but no concomitant measures of total body eicosanoid synthesis are available.[44,45] It is possible that linoleate lowers the blood pressure through a mechanism independent of eicosanoid synthesis. ω3 Polyunsaturated fatty acids are found in fish oil and can be metabolized to PGI_3 and TXA_3. The vasodilator effect of PGI_3 is comparable to that of PGI_2, but TXA_3 is a much weaker vasoconstrictor than TXA_2.[46] Knapp and FitzGerald found that supplementing the diet with high doses of fish oil increased the excretion of the major urinary metabolite of PGI_3 and lowered the blood pressure in human hypertensive subjects.[47] The time course of increased PGI_3 synthesis, however, was different from that of the decrease in blood pressure: PGI_3 synthesis increased before the blood pressure fell and returned toward normal when the blood pressure effect was maximal.

It is, therefore, unlikely that changes in blood pressure after the inhibition or stimulation of eicosanoid synthesis can be explained by simple changes in resistance vessel caliber due to vasoconstrictor and vasodilator eicosanoids.

Renal Eicosanoids in Hypertension

The characteristic functional vasoconstriction of hypertension occurs in the kidney to an equal or greater extent as in other vascular beds.[48] Indeed, some studies in humans[49] and spontaneously hypertensive rats[50] suggest that renal vasoconstriction precedes hypertension, thereby meriting consideration in the pathogenesis of hypertension. One possible mechanism is an increased tubular sodium reabsorption caused by a reduced peritubular capillary pressure, consequent upon a higher filtration fraction.[51]

Given the potent vascular actions of eicosanoids, it seems reasonable to look for a deficiency of vasodilator or an excess of vasoconstrictor eicosanoid synthesis in hypertensive kidneys. Shibouta and associates found that renal cortical slices from young spontaneously hypertensive rats in the prehypertensive stage produced more TXA_2 than those from Wistar Kyoto controls.[52] Kawaguchi and coworkers confirmed this and also found slight, lesser increases in PGI_2 synthesis.[53] The ratio of vasoconstrictor (TXA_2) to vasodilator (PGI_2) eicosanoid synthesis was increased.

Such in vitro studies measure the synthetic capacity of kidneys and may not reflect the actual synthesis in vivo. Moreover, they are not feasible in human hypertension. The urinary excretion of prostaglandins and their hydrolysis products appears to reflect synthesis and has been used to assess differences between patients with hypertension and those without.

The evidence for urinary 6-keto-$PGF_{1\alpha}$ and TXB_2 excretion rates reflecting a renal synthesis of PGI_2 and TXA_2, respectively, will be briefly reviewed. First, when large doses of TXB_2 are injected intravenously, only about 3.5% is excreted in the urine unchanged.[54] Similarly, only about 14% of a large—1 to 5 ng per kg per minute—intravenous infusion of PGI_2 was excreted as 6-keto-$PGF_{1\alpha}$.[55] These doses should produce plasma levels that are much higher than those found under physiologic conditions. Indeed, the "normal" circulating levels of 6-keto-$PGF_{1\alpha}$ and TXB_2 are vanishingly low.[34,56] Second, we have found that low doses of aspirin—0.5 mg per kg per day for a week—reduce platelet TXB_2 production by 97% but do not change the amount of basal or stimulated urinary excretion of TXB_2 or 6-keto-$PGF_{1\alpha}$.[57] This suggests that little of the TXB_2 in urine is derived from platelets. Because urinary TXB_2 and 6-keto-$PGF_{1\alpha}$ excretion rates change in parallel[41,57] when stimuli or inhibitors are given, it seems likely that they come from a common tissue—the kidney. Finally, unlike PGE_2, little TXB_2 and 6-keto-$PGF_{1\alpha}$ enter the urine from nonrenal sources.

Using these excretion rates, one group found decreased renal PGI_2 synthesis in hypertensive persons,[58] but these results have not been confirmed. In contrast, increased urinary TXB_2 excretion in human hypertension has been noted by two groups.[59,60] In our study, the difference between hypertension and normotension was magnified when renal eicosanoid synthesis was stimulated by adding furosemide.[60] More recently we found that older humans (aged 50 to 70) whose blood pressures averaged 130/80 mm of mercury excreted more TXB_2 after receiving furosemide than did younger persons (aged 20 to 30) whose blood pressures averaged 110/68 mm of mercury.[61] It is thus possible that increased renal TXA_2 production contributes to the increase in renal vascular resistance seen with aging.[48]

Effects of Thromboxane Synthesis Inhibition

The recent introduction of drugs that specifically inhibit thromboxane synthesis offers the opportunity to examine the physiologic significance of a change in the ratio of TXA_2 to PGI_2 synthesis. Inhibiting thromboxane synthase may not only decrease thromboxane activity but increase prostacyclin synthesis by diverting endoperoxide metabolism toward PGI_2.[62] We found that the use of furegrelate, a thromboxane synthase inhibitor, increased the urinary excretion of 6-keto-$PGF_{1\alpha}$ after the stimulation of renal eicosanoid synthesis with furosemide.[63] Furthermore, plasma renin activity was increased, consistent with increased renin release due to PGI_2 formation. More recently we found that administering furegrelate could reverse the renal vasoconstriction of angiotensin II.[64] This suggests that angiotensin II stimulates vasoconstrictor as well as vasodilator eicosanoid synthesis and that the final effects on renal vascular resistance may be the algebraic summation of all these influences (Figure 2). If the tendency to produce more TXA_2 were increased in the kidneys of hypertensive persons, then a given stimulus such as angiotensin II or norepinephrine should produce relatively greater vasoconstriction. Thromboxane synthesis inhibition may be of benefit in reversing this tendency. Indeed, thromboxane synthesis inhibition delays the onset of hypertension[65] and reduces the blood pressure in spontaneously hypertensive rats.[66,67]

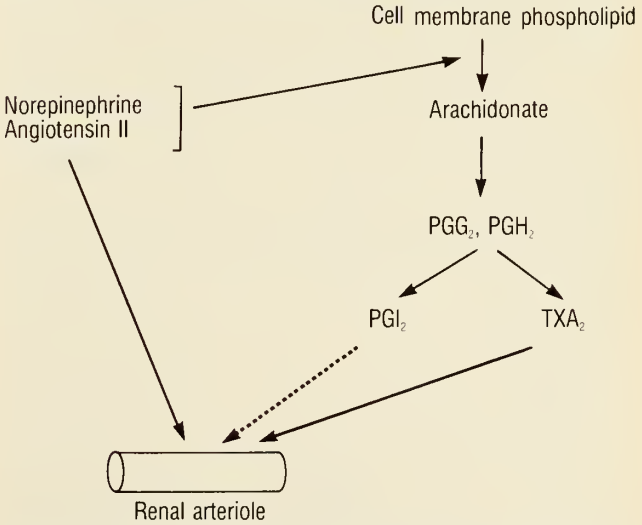

Figure 2.—The relation is shown between vasoconstrictor stimuli (angiotensin II, norepinephrine) and vasodilator (PGI_2) and vasoconstrictor (TXA_2) eicosanoids. The effect on renal vascular resistance is the sum of vasoconstrictor **(solid arrows)** and vasodilator **(dashed arrows)** influences. PG = prostaglandin, TX = thromboxane

Conclusion

In summary, it appears that the renal synthesis of TXA_2 is increased in some hypertensive persons and in some genetic animal models of hypertension. This might be responsible for the increased renal vascular resistance and suppressed plasma renin activity of hypertension. Specific thromboxane synthesis inhibitors can reverse this putative fundamental abnormality. Further research is necessary to compare such agents with traditional antihypertensive therapy.

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Non-A, Non-B Hepatitis

Discussant
THOMAS N. DEWAR, MD

This discussion was selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from a transcription, it has been edited by Homer A. Boushey, MD, Professor of Medicine, and Nathan M. Bass, MD, PhD, Associate Professor of Medicine, under the direction of Lloyd H. Smith, Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine.

HOMER A. BOUSHEY, MD*: *Non-A, non-B hepatitis, an important cause of morbidity and mortality from liver disease, has until recently been defined by the lack of an identifiable causative agent. The discovery of the hepatitis C virus—undoubtedly the most significant recent advance in hepatitis research—represents only the beginning of a new understanding of this disease and its epidemiology. This conference's review of non-A, non-B hepatitis and the impact of the hepatitis C virus discovery will be given by Tom Dewar, MD, who has served with dedication, tact, good humor, and a quiet insistence on excellence as a chief medical resident over the past year.*

THOMAS N. DEWAR, MD†: The term "non-A, non-B (NANB) hepatitis" is inherently unsatisfying intellectually as it immediately reveals the limited understanding of this clinical disorder; it is always preferable to identify a disease by what it is rather than what it is not. Nonetheless, despite the magnitude of this clinical problem and much investigation, this term will undoubtedly remain until all the infectious agents causing hepatitis are discovered. In this review, I describe aspects of the epidemiology and clinical features of NANB hepatitis in industrialized countries, outline the experimental approach leading to the identification and characterization of the "hepatitis C" virus (HCV) and its role in NANB hepatitis, and discuss what is known about preventing and treating this disease.

I will limit my discussion of NANB hepatitis largely to the form that occurs in industrialized countries. The enterically transmitted form of NANB hepatitis, now known as "hepatitis E," is a topic deserving a separate review.

Historical Background

Viral hepatitis has plagued humanity for a long time. Descriptions of jaundice are found as early as the fifth century BC, and Hippocrates commented on its features as well. In the latter half of the 19th century, the disorder was thought to be due to obstructed biliary outflow as a result of duodenal inflammation. This persisted until after World War I, when it was challenged by several groups based on their observations of postmortem liver specimens.[1] In retrospect, it is apparent that outbreaks of parenterally transmitted hepatitis occurred in the late 19th and early 20th centuries as a result of new therapies such as vaccination, insulin therapy, and iatrogenic malaria for the treatment of neurosyphilis. The expansion of transfusion technology during World War II led to widespread outbreaks of posttransfusion hepatitis. In 1947 McCallum proposed a term to describe two clinically distinct viral hepatic infections, namely hepatitis A and hepatitis B.[2]

Early investigations into the etiology of these infections were frustrating and slow; it was not until 1965 that Blumberg and others were able to isolate the "Australia antigen" as a marker of hepatitis B infection.[3] Feinstone and coworkers isolated the 27-nm hepatitis A viral particle and developed a serologic assay for this agent in 1973.[4] By 1975, accurate diagnostic techniques for both hepatitis A (HAV) and B (HBV) viruses had been achieved. It soon became apparent that at least one and probably two or more other agents could also cause hepatitis. The nature of these other agents remained unclear until the discovery by Choo and associates of a marker for a third virus that appears to be largely responsible for the ongoing problem of sporadic and posttransfusion hepatitis in the United States.[5]

Epidemiology

The large body of information about the prevalence and incidence of this disease, generated in the absence of a known etiologic agent or a precise diagnostic test, can be cumbersome and frustrating. Initial attempts to understand NANB hepatitis focused on defining its epidemiology in several clinical areas. Unfortunately, published studies have varied widely in their patient populations, the rigor of their follow-up, and their inclusion and exclusion criteria. In broad principle, patients were excluded from study if other conditions known to cause liver disease were found (Table 1).

The multitude of studies that examined idiopathic, presumed infectious, liver damage varied widely in the precision with which they defined their patients. Early studies often attributed any abnormalities to presumed hepatotoxic drugs or toxins such as ethanol, even when these assumptions were made in the absence of strong historical corroboration. The most reliable data come from carefully compiled series, rather than individual patients. Three often-cited sources of information are the Centers for Disease Control surveillance data, the sentinel counties study,[6] and the Baltimore case-control study.[7] These studies have helped define the scope of NANB hepatitis in the United States and illustrate the difficulty in obtaining valid data from small and anecdotal series.

The data from the sentinel counties study indicated an incidence of 4 to 10 cases of NANB hepatitis per 100,000

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(Dewar TN: Non-A, non-B hepatitis. West J Med 1990 Aug; 153:173-179)

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ABBREVIATIONS USED IN TEXT

ALT = alanine aminotransferase
HAV = hepatitis A virus
HBcAb = hepatitis B core antibody
HBV = hepatitis B virus
HCV = hepatitis C virus
NANB = non-A, non-B
NIH = National Institutes of Health
UCSF = University of California, San Francisco

population. Non-A, non-B hepatitis accounted for 20% to 40% of all cases of viral hepatitis (Table 2).[6] This study is important for at least two reasons. It involved five disparate populations in different areas of the country, and all the patients underwent intensive serologic testing. In contrast, during the same period, only 5% of cases reported nationally to the Centers for Disease Control were attributed to the NANB agent.[8] Less than half of these patients were screened appropriately for both HAV and HBV infection. Given these facts and considering that as many as 75% of cases may be anicteric, it is clear that the prevalence of NANB hepatitis is often substantially underestimated.

Non-A, non-B hepatitis occurs in a bimodal age distribution, one peak occurring in the third decade—all viral hepatic infections occur most commonly in this age group—and the second peak in the sixth and seventh decades, probably reflecting the increased use of blood transfusions in this age group. Most data indicate an equal sex incidence of infection.[8]

The Baltimore case-control study identified several risk factors for acquiring this infection (Table 3).[7] As with HBV infections, blood transfusion, parenteral drug usage, and close personal contact with infected persons were the strongest risk factors. No unique epidemiologic factors for NANB hepatitis have been described. Compared with controls, patients with NANB hepatitis were more likely to report a previous episode of hepatitis. These patients were also found to have a significantly higher incidence of previous HBV infection but not of HAV infection.[7]

With the imminent widespread availability of a method for detecting HCV infection (discussed later), our knowledge of the epidemiology of NANB hepatitis is likely to improve greatly in the near future. The effects of NANB hepatitis, however, have been particularly important in several specific clinical areas, some of which will be discussed, and it is useful to review the clinical data before and after the introduction of the HCV antibody assay.

Posttransfusion Hepatitis

Posttransfusion hepatitis remains a major public health problem in the era of modern medicine. In 1989 the San Francisco Irwin Memorial Blood Bank transfused about 115,000 units of blood (Cherie Evans, MD, oral communication, January 1990). Established data indicate that this therapy is associated with 3 to 6 cases of NANB hepatitis per 1,000 units of transfused blood. This estimate includes anicteric and asymptomatic cases of posttransfusional hepatitis and implies that 7% to 10% of all transfused patients will have exposure to NANB infectious agents.[9] Errors in technique and hepatitis B screening still occur, but the vast majority (> 95%) of posttransfusional elevations in routine liver enzyme values remain unexplained. The development of third-generation testing for hepatitis B has all but eliminated this agent as a cause of posttransfusional hepatitis. In 1985 Alter reported that not a single case of transfusion-associated hepatitis B had occurred in four years at the National Institutes of Health (NIH).[10] In the United States, the most successful means of decreasing the posttransfusional spread of NANB hepatitis has been the adoption of "volunteer-only" donor pools. Several studies have looked at this problem and reported at least a 2.5-fold increased risk of NANB hepatitis when commercial blood was used. The pooled results are even more impressive, showing a 28% risk of posttransfusional hepatitis compared with the 7% rate in volunteer-only blood donor programs.[10] With the development of an assay for antibodies directed against an antigen of the hepatitis C agent, it has been discovered that this particular agent accounts for approximately 80% of the cases of chronic posttransfusion NANB hepatitis.[11] Specific aspects of this assay and the epidemiology of the HCV infection in transfused patients are discussed further in subsequent sections.

Drug Addicts

The observation that some patients with NANB hepatitis had three or more distinct episodes of infection provided some of the first evidence that at least three hepatotropic viral agents existed. In 1977 Mosley and colleagues monitored 30 episodes of hepatitis in 13 intravenous drug abusers and found that 7% of infections could be attributed to HAV infection, 40% to HBV, and the remaining 53% to an NANB agent. Furthermore, 10% of the patients with NANB hepatitis had two or more distinct episodes of the infection.[12] In Sweden, Iwarson and co-workers found that

TABLE 1.—*Exclusion Criteria for the Diagnosis of Non-A, Non-B Hepatitis*

Toxic agents such as alcohol and anesthetic agents
Hemodynamic insults such as right-sided heart failure, sepsis, and shock
Metabolic liver disease such as hemochromatosis and Wilson's disease
Biliary tract disease
Known infectious agents including hepatitis A, B, and delta infections; Epstein-Barr virus and cytomegalovirus infections; and other bacterial, fungal, and parasitic agents known to damage the liver.

TABLE 2.—*Incidence and Relative Frequency of Non-A, Non-B Hepatitis in Different Areas of the United States**

County	*Incidence†*	*Relative Frequency, %*
Denver, Colo	10.2	27
Jefferson, Ala	6.0	24
Orange, Calif	8.3	26
Pinellas, Fla	4.0	20
Pierce, Wash	6.8	36

*Modified from Francis et al.[6]
†Per 100,000.

TABLE 3.—*Risk Factors for Non-A, Non-B Hepatitis**

Risk Factor	*Adjusted Odds Ratio*	*P Value*
Blood transfusion	13.6	< .05
Parenteral drug abuse	10.9	< .05
Health care-related work	1.7	NS
Direct patient care	3.9	< .05
Personal contact	12.8	< .05
Raw shellfish ingestion	3.1	< .05

NS = not significant

*Modified from Alter et al.[7]

25% of the 77 episodes of hepatitis in a cohort of 33 drug abusers could be attributed to NANB infection. They also noted two distinct episodes of NANB hepatitis in one patient.[13] Neither study, unfortunately, provided much follow-up information about these patients, particularly regarding the development of chronic liver disease. Both series found that NANB hepatitis was associated with milder clinical disease and lower peak elevations of serum bilirubin and hepatic aminotransferase levels than was HAV or HBV infection.

Hemodialysis

Non-A, non-B infection has emerged as a significant problem for both dialysis patients and staff. Galbraith and associates reported on an outbreak in a hemodialysis unit involving 29 patients.[14] Seven patients had two discrete episodes, and evidence of chronic liver disease developed in eight. Between 10% and 15% of patients undergoing dialysis may have chronically elevated levels of alanine aminotransferase (ALT). Another center reported an annual incidence of NANB hepatitis of 5.8% for patients and 0.8% for staff.[15] Again, because approximately three quarters of infections are anicteric, the long-term consequences of this disease are much more important than the often subclinical acute infection. Parenteral transmission appears to be the major mode of transmission, although the occupational reporting of needle-stick and blood exposure has not always correlated with subsequent infection, leading to speculation that other modes of transmission may exist. Garibaldi and associates did not find the prophylactic use of immune serum globulin effective in preventing disease in dialysis patients. The absence of secondary infections among family members is consistent with the hypothesis that this infection is transmitted by percutaneous and parenteral but not sexual contact in this population.

Renal Transplantation

Ware and associates reported 72 episodes of NANB hepatitis in 62 (38%) of 162 renal transplant patients.[16] In their population, several possible hepatotoxic insults were identified, but these investigators attributed 26% of acute and 71% of chronic elevations of liver enzyme levels to NANB viral infection. They found that 30% of patients with chronic NANB infection progressed to cirrhosis or hepatic failure. LaQuaglia and co-workers noted a 93% progression to chronic infection if exposure occurred within the first postoperative year versus a 64% incidence of chronic disease if the patient was infected after the first year of immunosuppression.[17] Interestingly, they noted that the development of chronic NANB infection was associated with a higher mortality (45% versus 16% at the end of the study) but that this was an indirect association; these patients did not die of liver failure. Finally, these investigators speculated that NANB infection, like cytomegalovirus infection, may be immunosuppressive. They reported higher allograft survival rates with NANB infection and suggested using a less intensive immunosuppressive regimen for infected persons. Recently the renal transplant group at UCSF has used the new serologic assay for hepatitis C antibody to screen 180 randomly selected renal transplant patients and found the prevalence of HCV antibodies to be 12% in this population. They also found that infection with HCV appeared to be more benign than with HBV in this population. Again, there was some evidence that this infection was immunosuppressive; there were no graft failures, and only one episode of rejection occurred in the patients with HCV infection.[18]

Health Care Workers

Health care workers have been a particularly difficult population to study, owing to the high number of asymptomatic infections. There have been convincing case reports of NANB hepatitis acquired through needle-stick injuries,[19,20] but prospective information similar to that being obtained for HIV exposure is lacking. This remains a significant issue, however, and given the greater prevalence of the NANB hepatitis agent(s), the risks to health care workers of acquiring clinically significant and, ultimately, even fatal NANB infection may be greater than those of HIV infection developing, despite the greater attention the latter has received in both the scientific and lay press.

Nonparenteral Transmission

Most of our information about the nonparenteral transmission of NANB infection comes from nonindustrialized nations. Studies are widely diverse in their populations and results and suggest that NANB infections account for 6% to 46% of sporadic hepatitis cases. In the United States, NANB hepatitis accounts for 15% to 30% of cases of sporadic hepatitis in adults and half those percentages in children.[21]

The role of sexual contact is unclear. In well-studied homosexual populations, NANB agents account for less than 10% of hepatitis cases and both HAV and HBV remain a much larger epidemiologic threat.[22,23] Alter and colleagues were the first to show that heterosexual contact could result in the spread of NANB hepatitis.[24] Nonetheless, it appears that NANB hepatitis is the least sexually transmissible of the three major viral hepatic infections.

Similarly, the role of perinatal transmission is unclear. One study found a 50% incidence of elevated liver enzyme levels in infants born of mothers with NANB hepatitis during pregnancy. As in adult cases, they noted milder disease in affected infants than in infants with perinatally acquired hepatitis B infection. These investigators recommended that immune serum globulin be given to all infants born of mothers with NANB hepatitis at birth and at 1 month of age.[25]

Cases of infection acquired through household contact have been reported in mental institutions,[26] in families,[27] and in other communal living situations. The numbers of patients in these reports were small, and the route of transmission was unclear.

On the other hand, epidemics of NANB hepatitis have clearly proved the existence of at least one enterically transmitted agent. The best studied epidemic to date was an outbreak in New Delhi, India. This involved more than 35,000 cases and was first reported in 1955. This epidemic was initially attributed to HAV infection, but several atypical features became apparent, including a longer incubation, an older population, the absence of secondary cases, an increased incidence of cholestasis, and an increased case-fatality ratio of 10%, particularly among pregnant patients.[28] Similar outbreaks have been described elsewhere in Asia and Africa. An enterically shed 27-nm, viruslike particle distinct chemically and immunologically from hepatitis A and capable of transmitting this form of NANB hepatitis, hepatitis E, has been identified[29] and cloned.[30] To date, epidemic NANB hepatitis has not been reported in North America.[31]

Clinical Features

Unfortunately, there are no specific clinical features of NANB hepatitis that uniformly distinguish it from the

other types of viral hepatitis. It does have some features, however, that collectively serve to distinguish it from HAV and HBV infections. The incubation period—mean, 7 weeks—intermediate between that of HAV and HBV infections, was one of the first of these features noted by clinicians.[21] This was also the average incubation period for posttransfusional hepatitis during the 1960s. Thus, NANB hepatitis was probably the most common cause of posttransfusional hepatitis even before the introduction of serologic markers for HBV infection. Patients with NANB hepatitis tend to have a milder form of acute disease. As a reflection of this, 60% to 85% of patients are anicteric, compared with 0% to 50% of those with HBV infection.[21,32] On the other hand, parenterally transmitted NANB hepatitis has a greater tendency to progress to chronic infection, with as many as two thirds of patients with posttransfusion hepatitis having elevated liver enzyme levels after six months.[21] A carrier may be entirely asymptomatic and, owing to the fluctuating nature of the aminotransferase levels, may have normal ALT levels. Some populations have shown high carrier rates. In the Veterans Administration's posttransfusional hepatitis study, an analysis of patients who received blood transfusions from single donors suggested a 3% to 7% incidence of the carrier state in this population compared with 0.1% to 0.2% for HBV infection.[33(p371)] Chronic infection may progress to cirrhosis and hepatic failure in 10% to 20% of cases, but patients appear to be "healthier" with fewer complications of portal hypertension and liver failure than patients with chronic HBV infection.[8] Unfortunately, there are no clinical or pathologic features that have been clearly shown to predict a progression to chronic infection.

Patients with NANB hepatitis do not often manifest immune complex-associated extrahepatic features—arthritis or urticaria is rare, for instance—but NANB hepatitis is the most common cause of hepatitis-associated aplastic anemia.[34]

Fulminant hepatic failure has been reported in a variety of clinical situations involving NANB hepatitis. One recent series found that patients with fulminant hepatic failure due to NANB hepatitis had the worst outcome among those with viral infections.[35] In several reviews, NANB hepatitis accounted for 27% to 44% of cases of fulminant hepatic failure.[36,37] As a cause of the failure, NANB hepatitis is less common than HBV infection but considerably more frequent than HAV disease. These figures, however, may represent an underestimation of the contribution of HBV infection to the population with fulminant hepatic failure, as it is known that patients in failure may lose the surface antigen marker of HBV infection owing to the intense immune response that results in the profound hepatic damage. Thus the mortality attributed to NANB infection may not be as high as earlier studies suggested. One important, frequently observed feature of chronic NANB hepatitis is the waxing and waning of serum aminotransferase levels. This is unusual in both HAV and HBV infections and has greatly complicated the evaluation of patients with NANB hepatitis by making it difficult to distinguish a new case of hepatic infection from flares in chronic disease.

Pathophysiologic Features

Because few patients with acute hepatitis undergo liver biopsy, there is not a large body of information on the histologic features of NANB hepatitis. Dienes and co-workers reported that liver biopsy specimens from these patients had a peculiar pattern of eosinophilic cytoplasmic "clumping" with microvesicular steatosis and activated sinusoidal cells.[38] They also commented on the absence of prominent portal or parenchymal inflammation. Another group reported on the specific finding of a "piling up" of the bile ductular cells without disruption of the basement membrane. They also noted that 85% of patients with this finding progressed to chronic infection.[39] It has already been mentioned that patients in the New Delhi epidemic frequently had a cholestatic pattern on biopsy specimens, an unusual finding in HBV or HAV infection. Unfortunately, these microscopic findings are not sufficiently sensitive or specific for NANB viral infection to aid in the diagnosis.

Many researchers have proposed a link between NANB hepatitis and hepatocellular carcinoma. It is recognized that 5% to 28% of patients with hepatocellular carcinoma have no serum markers of HBV infections.[40] On the other hand, the HBV genome has been found in DNA extracted from the tumors of as many as 50% of patients with hepatocellular cancer without serum markers of previous HBV infection.[41] Recently, with the availability of the HCV antibody, two separate groups[42,43] have reported an approximately 70% prevalence for HCV antibody in patients with hepatocellular carcinoma and no serologic evidence of hepatitis B exposure. In addition, the Milan group speculated that acquiring infection with both HBV and HCV agents increases the risk even further of hepatocellular cancer developing.[43] Finally, a substantial portion of patients with primary liver cancer lacks serologic evidence of exposure to either HBV or HCV. This has led to speculation that a second NANB agent may be present in these patients.[44,45]

As mentioned earlier, there have been no consistent indices of immune activation or immune-mediated hepatic damage in patients with NANB hepatitis. A T-cell defect has been described, with an increase in the T-cell helper-suppressor ratio, which may explain the previous observation of increased allograft survival in renal transplant patients with NANB hepatitis.[46] These observations led Dienes and associates to hypothesize that the NANB agent(s) is directly cytopathic to the liver, in contrast to the hepatitis B virus.[38]

The Discovery of Hepatitis C

The breakthrough in the search for a specific etiologic agent as well as a method to specifically diagnose and follow the course of NANB hepatitis as a distinct disease—the discovery of the hepatitis C virus—was achieved by applying innovative molecular biologic techniques. This exciting achievement was reported in April 1989 by Choo and colleagues.[5] They reasoned that the failure of conventional immunologic methods to reliably diagnose, characterize, or predict infection by NANB virus(es) reflected a low level of viral antigen expression in infected patients, rather than the absence of antibody formation. They devised a scheme (Figure 1) to isolate the nucleic acid material of the putative hepatitis C viral agent that made no assumptions about the nature of the virus (such as whether the viral genome was RNA or DNA), but only that in persons who had chronic NANB infection, an antibody response would develop to one or more viral epitopes. The starting material used to isolate the viral genome was chimpanzee serum that had been shown to be capable of transmitting HCV infection after significant dilution; that is, it possessed a high, infectious titer. The isolation scheme used the enormous sensitivity of modern cloning techniques to recover a complementary DNA (cDNA) clone that produced viral antigens that reacted with an antibody in the serum of a patient with NANB hepatitis. Their original report included the validations and characterizations shown in Table 4.

Choo and co-workers next cloned this cDNA probe into yeast so as to produce a fusion polypeptide containing human superoxide dismutase and viral antigens. This product, C100-3, could be produced in large quantities, purified, solubilized, and used to coat wells in microtiter plates. Anti-HCV antibodies in serum placed into these wells bind to the viral antigens, a reaction that is easily detected. Thus, a simple assay for HCV infection was established, providing for the first time a method to specifically characterize the epidemiology of this form of NANB hepatitis. The authors concluded that the hepatitis C virus was likely a member of the togarvirus or flavivirus family based on the aforementioned results and previous data indicating that the virus is smaller than 80 nm and probably contains a lipid envelope.[47,48]

Epidemiology of Hepatitis C

The earliest clinical confirmation of this breakthrough appeared in a companion article by Kuo and colleagues.[49] These investigators used the HCV assay to analyze NANB hepatitis serum from patients in the United States, Japan, and Italy. They found that six of seven serum specimens from a serum bank at the NIH with an established ability to transmit NANB hepatitis were positive for the HCV antibody. Nine of ten blood units that had resulted in NANB hepatitis were positive. In addition, all ten recipients of these blood units seroconverted. Of Italian and Japanese patients with chronic NANB hepatitis, 80% had the HCV antibody, but only 15% of patients with acute disease seroconverted. This disappointingly low rate of antibody formation during the acute phase of the disease has been confirmed by other investigators as well. In cases of acute NANB hepatitis in Japanese patients that resolved without evidence of chronic infection, the HCV antibody was also often lost. In this study HCV antibody was also found in 58% of patients with nonparenterally transmitted NANB hepatitis. Finally, in New York City volunteer blood donors, it was observed that if the ALT level was normal and the hepatitis B core antibody (HBcAb) not present, the prevalence of the HCV antibody was 0.5%. This figure increased to 44% if the ALT value was elevated and the HBcAb was present.

Other groups have further defined the epidemiology of HCV infection. Esteban and associates studied Spanish patients with NANB hepatitis and found HCV antibody in 85% of patients with posttransfusion hepatitis, 62% of patients with cryptogenic cirrhosis, 70% of patients with hemophilia, and 70% of intravenous drug abusers.[50] Homosexual men and female sexual partners of drug abusers had seroprevalence rates of 8% and 6%, respectively, suggesting that the sexual transmission of this agent is not common. The authors noted an overall HCV antibody prevalence of 1.2% in healthy patients without HCV risk factors. Kühnl and co-workers screened German blood donors in urban, rural, volunteer, and commercial donor populations.[51] The highest seroprevalence rate they found was 0.83%, but, interestingly, they did not find an increased rate in commercial or repeat donors. If the ALT level was normal, the seroprevalence rate was 0.42%. Van der Poel and associates prospectively observed 393 patients who received 5,315 units of blood[52] and found 9 patients with NANB hepatitis, 4 of whom seroconverted by six months of follow-up. The assay had a sensitivity of 67% for detecting infected blood products. The authors also noted a strong correlation with HCV seropositivity and increased ALT levels but no correlation with the HBcAb status.

Alter and colleagues studied a prospectively obtained NIH cohort of patients with acute and chronic transfusion-acquired NANB infection following open-heart operations. They selected 15 patients with chronic NANB viral infection and 5 patients with acute (resolving) NANB hepatitis. The mean time to seroconversion was 15 weeks (range, 4 to 32 weeks). All patients with chronic NANB viral infection seroconverted, but only three of the five patients with a resolving NANB infection seroconverted. All of these patients lost their anti-HCV antibodies after a mean follow-up of four years. About 90% of the donor specimens that presumably transmitted the NANB infection were positive for the HCV antibody. Half of these specimens were positive for the antibody to the hepatitis B core antigen; a third of the specimens had an elevated ALT level.

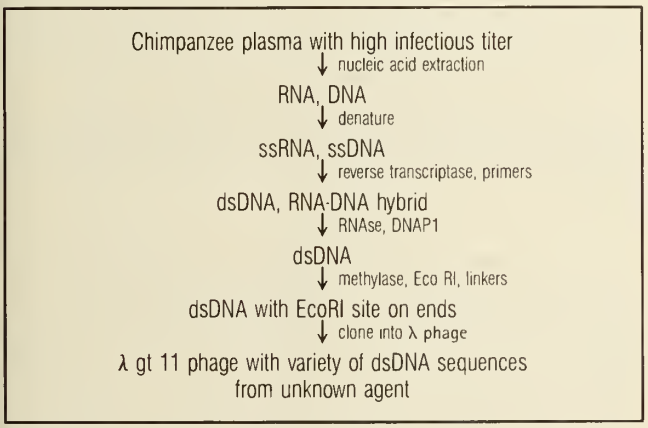

Figure 1.—The diagram shows the method of Choo et al[5] for isolating a hepatitis C cDNA clone. ds = double-stranded, RNAse = ribonuclease I, ss = single-stranded

TABLE 4.—*Characteristics of the Hepatitis C Genome*

- The cDNA clone did not bind to native human or chimpanzee DNA but did bind to total extracted RNA from infected liver, thereby confirming its viral origin
- The ability of the cDNA clone to bind to infectious material was lost after RNAse but not DNAse treatment, suggesting that the HCV agent is an RNA virus
- Only one strand of the cDNA clone bound to the extracted RNA, suggesting that the virus contains single-stranded RNA
- Southern blot analysis of the extracted RNA revealed that the RNA was 5,000 to 10,000 nucleotides long
- The RNA has a poly A 3′ tail or an adenosine-rich region, as evidenced by binding to oligo(dT) columns

DNAse = deoxyribonuclease, RNAse = ribonuclease I

Prevention

The most effective intervention to date for decreasing the spread of posttransfusion hepatitis has been the adoption of volunteer-only donor pools.[10] This would be expected to draw from a group of persons at low risk of having NANB viral infection. Unfortunately, screening prospective donors for information that would suggest a higher risk of exposure to the NANB hepatitis agent has not proved helpful. In particular, a history of jaundice, a previous transfusion, and increasing age have not been shown to correlate with the risk of transmitting NANB hepatitis.[53]

Laboratory Markers

Several laboratory markers have been investigated as surrogate tests to identify donors at higher risk of having NANB infection. Measurements of the serum levels of carcinoembryonic antigen and bile acids were too nonspecific to be clinically useful.[54] The alanine aminotransferase level in

donor blood, in contrast, has emerged as a useful marker for assessing the risk of transmitting NANB hepatitis. Transfusions involving one or more units with an ALT level of greater than 50 units per liter are associated with a 37.5% rate of infection.[55] Using this ALT level as a cutoff for rejecting blood donations has been criticized as wasteful because two thirds of rejected units would be lost on the basis of a false-positive result. Alter and co-workers calculated, however, that such a screening program would prevent a third of posttransfusion NANB hepatitis cases at a loss of only 1.6% of all units donated.[56] Both the ALT and HBcAb levels are currently used as surrogate markers at many blood banks. Because the efficacy of neither marker has been prospectively validated, this remains a controversial area of transfusion therapy.[32]

Prophylaxis

Studies using human serum immune globulin as prophylaxis during blood transfusions have yielded conflicting results. Kuhns and associates administered two doses of immune globulin prophylactically with blood transfusions to patients undergoing coronary artery bypass grafting.[57] They did not find immune globulin to be effective in decreasing the incidence of posttransfusion hepatitis. In contrast, Knodell and colleagues found that a single dose of immune globulin given preoperatively decreased the incidence of posttransfusion NANB hepatitis in two military hospital populations.[58] Seeff and Dienstag concluded that giving immune globulin decreased only the incidence of icteric NANB hepatitis and only if three or more units of blood were transfused.[59] More recently, Sanchez-Quijano and co-workers, using a newer preparation of immune globulin, found that giving it intramuscularly before and one week after transfusion was effective in reducing the incidence of NANB hepatitis (11% versus 3%).[60] They also noted that in those patients in whom NANB hepatitis developed despite prophylaxis, the disease was milder than in controls and did not progress to chronic infection.

Theoretically, the use of immune globulin may be more effective as prophylaxis after exposure to a smaller inoculum of infectious material, such as a needle-stick injury. In retrospective studies, Guyer and associates noted a decreased incidence of NANB hepatitis among household contacts,[61] and Simon and colleagues noted a decreased incidence among hemodialysis patients treated with hepatitis B immune globulin.[62] In 1979 Seeff and Hoofnagle proposed the prophylactic administration of immune globulin, 0.06 ml per kg, for HBV and NANB hepatitis for needle-stick recipients, sexual contacts of patients with NANB hepatitis, institutional contacts, and infants of mothers with NANB hepatitis.[63] The practice of administering immune globulin to all recipients of needle-stick injuries in the UCSF emergency department regardless of their HBV immune status reflects this recommendation.

Treatment

Administering acyclovir and corticosteroids has not been shown to be effective in the treatment of NANB hepatitis.[64,65] Two trials have been published recently that outline the experience with interferon alfa in the treatment of chronic NANB hepatitis.[66,67] In both studies the patient populations were defined initially by clinical, epidemiologic, and histologic criteria; subsequently, the prevalence of the HCV antibody was shown to be about 90% in both patient populations. Both studies noted an approximately 50% complete response rate (as defined by a return to normal of the aminotransferase levels) after six months of therapy. This was significant compared with placebo. In addition, the Hepatitis Interventional Therapy group noted a significantly higher response rate with higher doses of interferon.[67] Unfortunately, relapse after discontinuing interferon therapy was seen in 50%[67] and 80%[66] of the patients who responded to treatment. The side effects of interferon therapy were usually mild—flulike symptoms, fatigue, diarrhea—and self-limited. Side effects required a reduction in dose in a sixth of patients and resulted in a discontinuation of therapy in 4 of 135 treated patients. Efficacy was assessed on biochemical and histologic, not symptomatic, indices. In the NIH group, the patients were unable to predict whether they received interferon or placebo. The University of California, San Francisco, is currently participating in an ongoing multicenter, prospective, randomized trial of interferon alfa therapy for chronic NANB hepatitis, with dosages escalated for nonresponders and patients who relapse.

Conclusion

The advances in the understanding of HCV infection have been dramatic and long awaited. Clearly the black box that is non-A, non-B hepatitis is much smaller now. As discussed, however, experimental evidence suggests that at least one other parenterally transmitted hepatotropic viral agent exists; the full contribution of HCV infection to the larger disease category of NANB hepatitis remains to be seen. Undoubtedly, with the licensure of one or more assays to detect the HCV antibody imminent, an explosion of new epidemiologic information can be anticipated. It is amusing to speculate on the evolution of the name of this disease because the recent advances seem to require that the black box now awkwardly be called "non-A, non-B, non-C hepatitis."

Finally, there is reason to be optimistic that further breakthroughs in other areas of infectious disease will occur. The approach of Choo and associates certainly promises to have broader application. They concluded,

> As such, this represents cloning without prior characterization of the infectious agent. This approach should be relevant to studies of other diseases in which an unknown infectious agent (viral or otherwise) might be involved.[5(p362)]

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Stress and Hypertension

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In susceptible persons emotional stress results in immediate sympathetic stimulation, with a vasomotor response that results in a high-output state and elevated blood pressure; the vasopressor response seems to be transient. There seems to be no longitudinal epidemiologic validation of the attractive hypothesis that transiently elevated blood pressures are the prelude to fixed hypertension, however. The acquisition of hypertension by populations abandoning their traditional mode of living has been attributed to the sociocultural stress inherent in westernization, but these studies usually have not taken into account concomitants of this type of acculturation, such as dietary changes and increased body weight. The inverse relationship of blood pressure levels to education could explain the development of hypertension when aspiration to upward mobility is thwarted. The severity of perceived occupational stress relates inversely to blood pressure, suggesting that familiarity with a job renders the demands made by the work environment more predictable and less threatening in terms of vasopressor response.

(Mustacchi P: Stress and hypertension. West J Med 1990 Aug; 153:180-185)

Stress has aptly been called an "unclean" variable.[1] The precise nature of stress still eludes definition, and there is no consensus as to what stress encompasses.[2] Nevertheless, the widespread popularization of the concept and the research relating to stress have ensured that the association of stress and illness is regarded as a part of everyday experience.[2] In 1979, in a national survey, one of every two respondents nominated "emotional pressure, worry, anxiety" the "major likely" cause of high blood pressure, ahead of overweight (26%) and heredity (12%).[3] But there is still no medical agreement on whether stress is the most important[4] or an insignificant factor in the cause of hypertension[5] or whether the proposed relationship "remains to be shown."[6]

In this review I focus on studies selected for their possible relevance to our understanding of how stress relates to hypertension. They are presented under three headings that group several of the approaches identified by Vingerhoet and Marcelissen in stress research: emotional stress, which acknowledges interactional, transactional, behavioral, and life-style pathways; sociocultural stress, which relates vulnerability to sociocultural (macro)factors and other group differences; and occupational stress, which arises from work activities, the organizational structure of the work environment, or both.[7] These categories are not mutually exclusive, and studies reflecting more than one approach are discussed under the heading that, to me, seemed most germane to the substance of the relevant findings.

Emotional Stress

Stress is generally perceived to be an imbalance between environmental demands and a person's ability to meet them. Stress is not just an environmental condition but an interaction of a particular external environment and a particular person; thus, not every person will evaluate and react to a situation in the same way.

To be psychologically stressful, an event must result in a mental burden that will strain the functioning of the mind. To a large extent, psychological stress develops whenever newly acquired information does not fit comfortably into the established pattern of data already stored in our memory.[8] As we go through life, experience helps us develop a mental picture of our own self, of the external world in which we live, and of the relationship between the two. This mental picture acts as a map that guides us in making decisions when confronted with new information about the world around us.[9] Stress results when new information clashes with the prearranged mental pattern that over the years we have come to consider a truthful and dependable representation of the external world.

Although both desirable as well as undesirable changes in our environment call for adjustments, published data support the notion that mainly undesirable changes occasion emotional stress reactions.[10] If emotional arousal can be avoided, physical stresses such as cold, fasting, or exercise fail to elicit the neuroendocrine cascade associated with psychological stress.[11] Ironically, despite humanity's ability to now control hunger, cold, heat, and hard physical labor, we are still susceptible to distress due to frustration or to anything likely to threaten our well-being and security. We do not have to be starving, thirsty, wet, or cold to experience stressful emotional arousal with an activation of the limbic structures in the brain.[12]

Sympathetic activation is held responsible for the transient elevation in blood pressure observed during acute psychogenic stress such as forced mental arithmetic, when it is associated with increased heart rate, visceral vasoconstriction that exceeds muscular vasodilatation, and, more often than not, high cardiac output.[13-18]

It is unclear whether this hyperreactivity is related to intrinsic arterial and cardiac sensitivity or whether the central nervous system is more responsive in perceiving or processing stimuli by neurologic and biochemical mechanisms.[19] In any event, should attack or flight ensue, the resulting circulatory redistribution, favoring muscle and brain, transforms within seconds the resting circulation into a heart-muscle-brain perfusion system of greatest advantage as a defense reaction.[15,18]

Transient blood pressure rises are observed after exposure to acute physical or emotional stress in normotensive persons and in those with borderline, early, labile, or persistent hypertension.[20-26] The elevation can last from a few minutes under experimental conditions to a few days or longer in the case of major disasters or warfare.[25,27-31]

Similarly, competitive mental tasks induce sodium and fluid retention in young men with one or two hypertensive

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parents, the degree of retention being related to the magnitude of heart rate increase during stress.[32] This suggests sympathetic mediation that occurs in response to active challenges, such as problem-solving tasks and competitive games, but not during exposure to the more passive stress of observing a disturbing film.[33] Rofe and Goldberg described a clear-cut gradient in blood pressure values prevalent in Israeli women with exposure to different levels of war and terroristic dangers.[34] In the low-stress environment following the war, blood pressure values ceased to increase, whereas in the north of Israel where the state of war persisted, blood pressure values continued to rise. These observations seem to fit with Syme's concept that a person's perception of the "control of destiny" can be an important social determinant of disease.[35]

Anticipated and actual job termination or the uncertainty and threat incident to the nuclear accident at Three Mile Island are well-documented instances of perceived mental stress that has been accompanied by elevated rates of norepinephrine excretion persisting for a year or more.[36,37]

Blood pressure control is multifactorial, and probably there are many types of hypertension. The core of the mechanism of one of them seems to be angiotensin.[38] Of considerable interest are reports indicating that the sympathetic stimulation that occurs during psychological stress leads to renin secretion. This is observed in persons taking examinations and in caged rats exposed to a hungry cat.[39,40]

Because not every member of a stress-exposed population responds with the same rise in blood pressure,[41] important homeostatic mechanisms must be protecting those spared hypertensive changes. Genetic factors and coping style have been studied, the evidence being more substantial for the former than the latter. A genetic component is apparent from studies on blood pressure variations in twins and from the observation that of identical twins, the first to become hypertensive is the one with exposure to greater psychological stress.[42-46] There is also a familial aggregation of blood pressure and heart rate responses to behavioral stressors because offspring resemble their parents and siblings resemble each other.[47] The magnitude of the hemodynamic response appears to be genetically determined because it is least pronounced in normotensive controls without a family history of hypertension, maximal in persons with labile hypertension with one or two hypertensive parents, and intermediate in normotensive persons with at least one hypertensive parent.[16,17]

Regarding coping style, persons with hypertension have been described as having suppressed anger and hostile feelings that they frequently "act out," feel guilty about such behavior, or avoid guilt over the expression of anger.[48-52] Hypertensive persons who suppressed anger as part of their coping style had higher diastolic pressures than their hypertensive counterparts who expressed their anger and were more likely than nonsuppressors to remain hypertensive away from the stressful clinic environment.[49,53-57]

The reported association with coping style seems somewhat weakened by the observation that after controlling for age, social class, and obesity, only systolic pressure relates to suppressed anger in white men but not in African-American or white women.[58] No association was found by the prospective Tecumseh (Michigan) Community Health Study; neither suppressed anger nor guilt related directly to blood pressure.[59] Conflicting observations were also reported on the anxiety levels of anger suppressors and nonsuppressors.[52,57,60,61]

Reflecting the complexities that characterize this area of research, a study of a nationally drawn adult population sample found no association of psychological state and hypertension among people who had never been informed that they had hypertension.[62,63] After a one-year follow-up of some 10,000 hypertensive persons, researchers concluded that being so labeled does not necessarily produce negative psychological consequences.[64]

Evidence for a pathogenetic role of stress in human hypertension suffers from the limitations inherent in short-term observations; expanded longitudinal studies are indispensable for reaching valid inferences.[65] Nevertheless, these observations can be interpreted as showing that in labile hypertension and in some normotensive persons with a genetic risk for hypertension, central nervous system mechanisms can increase adrenergic and cardiovascular responses to the point of proving vasopressor. It is still unclear whether the initial stress-induced sympathetic drive is a prelude to fixed or established hypertension, and arguing against such an association is the observation that the prevalence of hypertension among Holocaust survivors was not increased in spite of the serious emotional stresses they suffered.[66]

We know that the excessive sympathetic drive characterizing the early phase of hypertension persists later in the disease when the cardiac output, but not the plasma norepinephrine level, returns to normal.[67,68] In both situations, hypertension is controlled by pharmacologic adrenergic inhibition. In the established phase of hypertension, both cardiac output and norepinephrine levels are normal, whereas the peripheral resistance becomes elevated.[66] Although the neurogenic aspects of the early stages of hypertension can be easily linked to limbic activation, the association is still indeterminate when we consider the conversion from a high cardiac output to a high resistance state.[69]

Sustained pressor responses occur in squirrel monkeys and in rhesus monkeys trained to avoid adverse stimuli.[70,71] In rhesus monkeys, hypertension was accompanied by a decreased 24-hour mean heart rate, suggesting that the pressure elevation might have been mediated by enhanced peripheral resistance. After a year, one study[72] but not another[71] reported the development of fixed hypertension. In baboons trained to maintain an elevated diastolic pressure for 12 hours a day by aversion conditioning, the blood pressure reverted to normal between sessions even after many months of training.[73]

As regards human hypertension, the suggestion that the transition from a high-output to a high-peripheral resistance state could be mediated by the presence in the central nervous system of a pressure-responsive feedback mechanism is attractive.[68] If, for some possibly behavior-related reason in hypertension, this center were reset to function at a slightly higher point, at first the "desired" pressure would be achieved by an enhanced autonomic cardiovascular drive.[74] Later, with increased arteriolar responsiveness, a continuing hypertensive state could be maintained with less sympathetic drive—with no need either for elevated cardiac output or for a heightened norepinephrine release. Accordingly, the behavioral aspects of hypertension would be contributing to the cause of this multifactorial disease, as well as to its consequences on target organs, where, for example, brain involvement may become manifest with personality changes.[75]

Sociocultural Stress

A trend toward normalization of elevated blood pressure values was reported in 1927 in medical missionaries who had moved from America to China where their work increased their sense of self-esteem.[76,77] In religious orders observing the vow of silence, reduced social interaction was considered an important factor in erasing the expected age-linked increase in blood pressure values.[78,79] In Texas, the low frequency of hypertension among Native Americans,

contrasting with the much higher frequency observed among Mexicans, whites, and African Americans, was attributed to their living in a less stressful environment.[80]

Other observations have linked a low rate of hypertension in Alaska, South America, and Africa to modes of life predicated on traditional cultural values and essentially devoid of technologic advances.[81-83] The overrepresentation of hypertension among urban Zulus was attributed to the added social stress incident to their frequent arrests and humiliations, something not experienced by their normotensive rural counterparts.[84]

Increasing age clearly was associated with hypertension in both urban and rural Zulus, but among city dwellers, hypertension also correlated with how long they had lived in an urban community; by implication, this correlated with how long before that they had abandoned their traditional tribal culture. There was no age-related hypertension reported for a nonwesternized tribe with strong cultural traditions living in the Brazilian tropical forest.[85]

After moving to an industrialized country, migrants from nontechnologic cultures have an increased frequency of hypertension and of its complications.[86] Westernized migrants also acquire the systematic age-related increase in the prevalence of hypertension similar to what is seen in industrialized countries such as the United States where, however, the age-corrected prevalence is still lower among foreign-born men than among native white Americans.[87,88]

The prevalence of hypertension also correlated with the degree of westernization in certain populations living in the South Pacific. The lowest risk status was observed in one of the most isolated islands more than 1,000 km from the next closest island.[89] The population of a Pacific atoll was examined before and after migrating to New Zealand. Migrants settled in urban centers where their diet changed and they consumed more proteins and carbohydrates. Blood pressures rose faster in male and female migrants than in their nonmigrant counterparts.[90] The degree of social interaction of migrants with New Zealand society correlated positively with their blood pressure values, suggesting the presence of a protective effect for migrants who remained outside the western culture.[91]

Migration involves other changes besides a fading of traditional values. Changes in diet and the acquisition of body weight are measurable variables that in migrating populations correlate well with the development of hypertension.[14,92-94] Conversely, male Falklanders moving from a developed society to a more traditional setting adopted a different life-style, resulting in a high level of habitual physical activity, less obesity, and a lower prevalence of hypertension.[95]

The increased susceptibility of African Americans to hypertension seems to have been first described in 1932.[96] Since then a number of studies have continued to document their higher prevalence of hypertension.[97,98] The hypothesis that stress raises hypertension prevalence is supported by the observation that the average blood pressures of African Americans living in high-stress areas where unemployment, crime, and crowded conditions are ongoing features of the environment are higher than those residing in low-stress neighborhoods.[48,99] Hypertension-related deaths may be overrepresented in high-stress areas,[100] but one study found no difference in the blood pressures of African Americans reporting different levels of perceived stress.[101]

The inverse relationship of blood pressure to education and social class is in keeping with the notion that in industrialized societies complex problem-solving and communication skills are essential in many work- and nonwork-related situations, and that these skills are gained chiefly through formal education.[102-104]

The inverse relationship could explain the pattern of hypertension most prevalent when an aspiration to upward mobility is thwarted, and hypertension develops in persons who ineffectively attempt to cope with difficult environmental stressors they erroneously think they can ultimately conquer.[104]

A person's perception that he or she can meet the demands of the environment through hard work and determination has been termed "John Henryism" after the 19th century African-American folk hero.[104] The hypothesis that persons scoring below the median on education but above the median on John Henryism would have higher blood pressures than any other group was verified not only in a predominantly African-American town in North Carolina but also among Dutch men.[104,105]

These observations suggest that beneficial factors conducive to vasopressor homeostasis are apt to be present in stable cultures that honor traditional norms and whose members feel secure in social roles to which early experience has adapted them, especially if aspiration for upward mobility is not thwarted.[106] Problems can arise when previously sanctioned behavioral roles lose their cogency and can no longer be used to express behavior.[4]

Occupational Stress

Basic to the development of occupational stress are threats that lead to feelings of insecurity and inadequacy.[107] There may also be an element of time pressure with the need to meet deadlines and to fulfill commitments at an accelerated pace. The feeling of distress associated with such situations becomes more intense when workers feel trapped at the receiving end of a command line that they cannot question. Notable stress reactions have been observed in workers confronted with conflicting directives often inherent in the ambiguity of their professional roles. For example, both school teachers and prison guards are responsible for the care of a segment of the population essentially outside the mainstream of society.[108] Society demands that children be taught to be self-sufficient, but society does not tell teachers whether children should be educated to become independent thinkers or simply be trained to fill positions in the economic structure of the country. Similarly, society has been unable to reconcile the need for keeping criminals out of circulation and for maintaining order and discipline in jails with the avowed aim of rehabilitation and a growing concern for prisoners' rights.

Prison guards and teachers caught in the crossfire of conflicting directives find themselves in ambiguous and stressful roles.[108] Nevertheless, neither California nor Washington State has an overrepresentation of deaths from stroke in these two occupational categories.[109,110]

Work with no real possibility for social interaction is always stressful. A typical example is the sawmill industry, where production technology depends on a moving belt over which workers have little control.[111] The situation is compounded by the presence of noise, itself a moderately powerful vasopressor.[111-114]

When the remuneration of workers is based on piecework rather than on a straight salary, production increases but physical discomfort, fatigue, and stress become progressively more prominent.[115] Among male hourly workers employed in noisy plants for at least 10 years, the prevalence of hypertension varied as a function of suppressed anger and three job stress indices—job future ambiguity, dissatisfaction with co-workers, and dissatisfaction with promotions.[116]

Of 388 eligible subjects, 215 employed hypertensive men and randomly selected controls completed a research protocol. After adjusting for 10 variables, a cross-sectional study

related job strain to diastolic blood pressure. In those aged 30 to 40, but not in those aged 41 to 60, job strain also related to left ventricular mass index.[117]

An increased frequency of hypertension in air traffic controllers was attributed to the demands of their jobs,[118] but a subsequent well-designed longitudinal study of 25,000 air traffic controllers, a study group six times as large as the one reported on previously, failed to detect any excess of hypertension among them.[119] Among air traffic controllers, both current and future hypertensive persons reported less life change distress than did persons with normal blood pressures.[120] Moreover, satisfaction with management was positively correlated with the risk of developing hypertension.[121] Perceived job pressure did not correlate with hypertension in the Tecumseh Community Health Study, in a study of San Francisco bus drivers, and in a study of Finnish white- and blue-collar workers.[122-124]

The blood pressures of men who participated in the Framingham study who were free of coronary artery disease during the eighth or ninth biennial reevaluation correlated with personal worries and marital disagreement on subjects such as money, in-laws, children, housekeeping, and sex, but not with work-related variables such as nonsupport from the boss, work overload, and occupational mobility.[125]

Another important longitudinal study determined the blood pressure trends of about 1,000 healthy aviation cadets and flight instructors.[126] Of these, 20% died in action during World War II. The survivors underwent periodic reevaluations over the subsequent 24 years. There was no increase in blood pressure with age. This is a rather remarkable finding considering their stressful work. Their war fatality rate of 20% conveys a measure of the life-threatening risks they had faced, but also in peacetime, the naval air pilot is confronted with extremely stressful duties. Increased levels of catecholamine and serum cortisol excretion document these pilots' awareness of risk and the intensity of their alarm reaction during flying assignments compared with control days.[127]

It has been suggested that the ability of the naval aviators to remain normotensive despite the potential stressor effect of their work environment reflects the fact that they had been thoroughly adapted from youth to the technologic demands of their occupation and of the social framework in which they spent most of their waking hours.[106] Similarly, adaptation to the special sophistication imposed by modern technology may explain the stability of heart rate and blood pressure of a group of surgeons, surgical nurses, and operating room technicians on operating days, even though on those days they exhibited increased excretion of epinephrine and norepinephrine that is considered a manifestation of increased stress.[128]

Based on the urinary excretion of 17-hydroxycorticosteroids, an even greater adaptation response was achieved by a group of medical corps personnel flying dangerous combat missions in a helicopter ambulance during the Vietnam War.[129] There was no difference in their 17-hydroxycorticosteroid levels on flying and on nonflying days; actually, they had a lower excretion of 17-hydroxycorticosteroid than a comparison group in the continental United States not having exposure to combat risk and war stress. The effective control of alarm arousal in the face of real and continued danger was explained at least in part by the perception of the humanitarian value of their work and the gratitude of the persons they rescued. We have no information on what happened to the blood pressure of these medical workers. It is likely that in the absence of emotional arousal, their blood pressures remained stable.

The demands made by the work environment might be perceived as simpler, more predictable, less threatening, and as a whole less stressogenic than the conflicts frequently present in personal life.

Discussion

Certain criteria of causality can be used in assessing the relation of stress to established hypertension.[130] Temporality requires that the cause precede the effect, a sine qua non in causality.[131(pp17-21)] Most of the reviewed studies are cross-sectional and thus do not lend themselves to analysis in terms of this temporal yardstick. One longitudinal study described an enhanced cardiovascular reaction to mental stress as a marker for future hypertension, but the studied population already had borderline hypertension.[132] Blood pressure values fell after those studied moved, presumably to a less stressful environment, and increased following major disasters, warfare, or migration to urban centers.[27-31,76,77,90,91] Conversely, studies of air traffic controllers, bus drivers, and Georgia workers linked higher blood pressure readings to lower levels of perceived stress.[120,123,133] Similarly, a long-term prospective study of naval aviators showed that they remained normotensive in spite of the stressful demands of their occupation.[126]

Biologic gradient refers to the presence of a dose-related response. Here, too, the reports are both scarce and conflicting. One study shows no differences in the blood pressure of persons reporting different levels of perceived stress[101]; another describes a direct relationship of stress with hypertension and hypertension resolving after stress ends,[34] whereas an inverse relationship was reported on other occasions.[120,122,123]

Consistency requires that the association was verified in different populations and under different circumstances. As regards the association of stress and hypertension, cross-sectional studies are generally consistent in describing a positive association, an inference supported by one longitudinal study,[125] but the conclusions reached by three other prospective studies discount the association.[119,122,123]

Strong associations are more likely to be causal than weak ones, because if they were due to confounding or some other bias, the bias would have to be even stronger and, presumably, more evident. The mean hypertension-related death rate among 45- to 54-year-old nonwhite men in high-stress counties in North Carolina was nearly twice that of their counterparts living in low-stress counties,[100] but there is no information regarding how much the observed difference in rates is influenced by differences in social class, a fairly powerful determinant of hypertension.[98,134] Independent of this possible confounding factor, the inverse relationship mentioned earlier introduces justifiable uncertainty on the putative strength of a direct association.[120,122,123]

Plausibility refers to the biological plausibility of a causal hypothesis. The hypothesis that stress can lead to sustained hypertension is plausible because it fits with the accepted concept that illness results when a susceptible host undergoes exposure to an adverse environment. Variations in individual susceptibility to hypertension and in the magnitude of sympathetically induced cardiodynamic responses to stress are well-documented observations compatible with the proposed etiologic hypothesis. Other plausible hypotheses have been advanced to explain the transition from the high-cardiac output state of labile and borderline hypertension to the normal output and raised peripheral resistance characterizing an established hypertensive condition. The transition could be mediated by structural arteriolar changes induced directly by increased cardiac output through hypertrophy of the arteriolar smooth muscle in response to higher blood pressures.[67] According to this view, the affected arterioles develop an al-

tered wall-lumen ratio and respond to vasoconstrictive stimuli more than do normal vessels.

Alternatively, certain behavioral characteristics could contrive to induce an increased sympathetic drive that eventually would lead to downward regulation of the adrenergic cardiac receptors, thereby reducing both cardiac responsiveness and output.[135] Unfortunately, there are still no longitudinal data regarding prehypertensives with hyperreactive sympathetic systems followed up until borderline and established hypertension develops through which either hypothesis could be tested and possibly validated.[5]

Specificity, which requires the ability to predict one of two interrelated factors from the existence of the other, does not apply to a multifactorial disease such as hypertension.

Conclusions

In susceptible persons stress causes a transient, sympathetically mediated rise in blood pressure. It is still unclear if repetitive or continuing stress will induce fixed hypertension.

Repetitive exposures to stress can result in habituation, with a consequent blunting of the sympathetic response and associated cardiodynamic changes. This is especially evident in the work environment where work-related stress is presumably better definable and more predictable than elsewhere. But the exact coping mechanisms on which we depend for dealing successfully with stress are still incompletely understood.

Plausible hypotheses linking stress to hypertension have been advanced, but the longitudinal information required for a satisfactory validation is not yet available.

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Epitomes

Important Advances in Clinical Medicine

Ophthalmology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in ophthalmology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers, or scholars to stay abreast of these items of progress in ophthalmology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Ophthalmology of the California Medical Association, and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
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Recent Developments in Radial Keratotomy

Radial keratotomy is a surgical procedure designed to correct nearsightedness (myopia). During the procedure, the surgeon uses a diamond-bladed micrometer knife to make spoke-like partial-thickness radial cuts in the paracentral and peripheral cornea to produce corneal flattening, which reduces myopia. In the early 1980s the operation was growing in popularity but had not been formally tested. In 1981 the National Eye Institute funded the Prospective Evaluation of Radial Keratotomy (PERK) Study to investigate the safety and efficacy, predictability, and stability of radial keratotomy. The PERK results and those of other studies have shown that almost all patients become less myopic with few serious complications. Those with less myopia had better results four years after the procedure. Approximately 75% of patients in the PERK study had 20/40 vision—unrestricted driver's license vision—or better without glasses, and 64% wore no optical correction. The predictability of results for an individual patient has been less than desired, however. New technology and surgical techniques are improving the predictability, and, as a result, about 80% of operated eyes now fall within the ± 1.00 diopter range, the ideal result being mild residual myopia (−0.50 diopters).

Based on results reported to date, the relative safety of radial keratotomy is documented. Severe vision-threatening complications have been rare, and the most common complications, although not insignificant, have been a loss of two or three Snellen lines of best corrected visual acuity. This occurred in 2.5% of the patients in the PERK study at four-year follow-up.

Surgeons doing radial keratotomy previously used 16 or more incisions; the PERK study used 8, and many surgeons are currently using 4 initial incisions. If an undercorrection occurs, the original incisions can then be lengthened or deepened, or additional incisions can be added. Further studies will be required to examine the effectiveness of these techniques in improving predictability.

All of the major radial keratotomy studies have reported the phenomenon of a continued progressive effect of the surgical procedure in some patients. From 15% to 31% of patients' operated eyes have had a continuing decrease of −1.00 diopter or more—a change toward farsightedness—from one to four years after the operation. There is speculation that this is associated with wound healing, and some data support an association between an incisional depth of greater than 90% of corneal thickness and instability. Follow-up results beyond five years will provide useful information regarding this problem.

In the longer term, two technologic applications may improve radial keratotomy results and its predictability. By the use of finite-element computer simulation of the cornea, the theoretic results of radial keratotomy can be studied. The correlation of theoretic and experimental results will lead to a better understanding of the biomechanics of the cornea and to better surgical techniques. In addition, computerized imaging of the corneal shape, videokeratography, allows more detailed study of the optical properties of the cornea after the surgical procedure.

The second new technology is using excimer lasers to do corneal operations. Two strategies that use pulsed 193-nm argon fluoride ultraviolet lasers to remove submicron amounts of tissue are being investigated. Laser keratomileusis involves reshaping the anterior surface of the cornea. The laser can also be used to make linear excisions, as in standard radial keratotomy, but wound healing remains a problem.

Altogether, about 15 different corneal surgical techniques to correct refractive errors are being investigated, and the field remains one of the most active and intriguing in ophthalmology.

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Current Uses of Collagen Shields

Collagen shields are biodegradable contact lens-shaped films made of porcine or bovine scleral collagen. After placement on the eye, naturally occurring enzymes in the tear film cause the shields to dissolve over a 24- to 72-hour period, depending in part on the degree of collagen cross-linking induced at the time of manufacture. Their use as a clinical tool in ophthalmology is now widely accepted.

Recent studies have proved the collagen shield to be an excellent vehicle for drug delivery to the eye. Dexamethasone, gentamicin, tobramycin, and vancomycin hydrochloride all have been shown to have equal or greater concentrations in the cornea, aqueous, and iris when a soaked collagen shield was placed on the eye as when hourly drops or subconjunctival injections were used. The shields also have been shown to enhance corneal epithelialization postoperatively and after corneal abrasions.

In light of this recent research, some ophthalmologists are now routinely using collagen shields soaked in antibiotics and corticosteroids postoperatively as a replacement for subconjunctival injections in cataract, corneal, and anterior segment procedures. Follow-up has shown these eyes to be less inflamed in the immediate postoperative period with less discomfort. Other potential applications are using the shield in treating bacterial corneal ulcers, enhancing the healing of persistent epithelial defects or neurotrophic corneal ulcers, and possibly as an adjunct to dry eye therapy.

The collagen shields' capability of drug delivery, protection, lubrication, and accelerating epithelialization makes them particularly useful in ophthalmic surgical procedures and should prove to be a valuable therapeutic tool.

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Botulinum Toxin for the Treatment of Blepharospasm and Strabisumus

In his pioneering work, Scott showed that an injection of small quantities of a purified reconstituted solution of botulinus toxin type A (Oculinum) into an extraocular muscle will cause a dose-related but temporary paralysis of the muscle. The drug is intended as a medical alternative to the surgical procedures currently used to treat blepharospasm and certain strabismus conditions. A chemically denervated muscle will cause a change in the position of the eye. With prolonged administration, some degree of contracture of the antagonist muscle is thought to occur, presumably resulting in a lasting alteration of ocular alignment.

The Food and Drug Administration (FDA) has recently granted premarket approval to botulinus toxin for treating blepharospasm and strabismus in patients at least 12 years old. Oculinum, which is a lyophilized form of purified botulinus toxin type A, blocks neuromuscular conduction. When injected in therapeutic doses, it produces a local denervation muscle paralysis that is useful in reducing the severe muscle contractions associated with blepharospasm. Botulinus toxin type A is administered by a subcutaneous injection at specific sites around the eye. Its beneficial effects last an average of 12½ weeks. Injections may need to be repeated, and this should not be viewed as a failure.

In one clinical study, botulinus toxin type A was administered to 27 patients with essential blepharospasm, 26 of whom had been treated unsuccessfully with benztropine mesylate, clonazepam, baclofen, or some combination of the three. Of the 27 patients, 25 reported improvement within 48 hours of the initial treatment. One patient's blepharospasm was later controlled with a higher dose. The other patient reported only mild improvement. In an open trial to test the effectiveness of the antitoxin in treating strabismus, 667 patients with strabismus were given one or more injections of the drug. Of the 667 patients, 55% had improved to an alignment of ten prism diopters or less when evaluated six months or more after injection. To date, 4,000 patients have received more than 7,000 injections to treat strabismus. Likewise, in the treatment of blepharospasm, more than 4,000 patients have received well over 7,000 treatments.

Although some practice with the technique is important, once the skill is acquired, it is a relatively safe office procedure for treating strabismus that requires only an injection of the drug into the extraocular muscle. Although successive treatments may be necessary, the success rate approaches that of standard strabismus surgical procedures.

At this time, the FDA has released botulinus toxin type A for the treatment of strabismus in patients 12 years of age and older, excluding it for the treatment of childhood strabismus and particularly for infantile esotropia. Currently, however, there are research protocols in effect for the treatment of congenital esotropia, and early reports indicate promising results.

Transient ptosis has been reported as a side effect in about a third of the patients, and some investigators have reported unexpected hypertropias at a rate of 15%. Other complications that have been reported are 9 cases of scleral perforation, none of which resulted in retinal detachments, and 15 cases of retrobulbar hemorrhage, again with no permanent disability resulting.

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Evaluating Functional Vision

Vision traditionally has been evaluated using a Snellen chart and notation. The chart presents black and white letters of different sizes that are scaled to quantify the resolution of the eye. Patients frequently complain that their vision deteriorates as they age and that they have trouble seeing to drive at night. The Snellen eye chart often reveals normal acuity in these persons. The standard eye chart was developed during the Civil War period before the invention of the electric light bulb or high-speed driving. Disorders such as cataracts, diabetes mellitus, and macular degeneration may not be evaluated properly with the existing eye chart. The term functional vision has been coined to describe what we need to test. This denotes the visual ability to perform under various lighting situations.

The Snellen system tests the resolution of our eyes with black letters on a white background. Most of our vision is achieved by detecting the differences between borders, however. The degree that a person can determine the sub-

tlest change gives us an important measure of the quality of vision. This kind of testing is called contrast sensitivity. There are two clinical testing systems in use today. The first presents to the patient sine wave gratings in which either the frequency or the contrast can be changed. Each eye is independently shown a target of vertical gratings. The grayest resolvable grating represents the contrast sensitivity for that frequency. The gratings are then made narrower and the entire process is repeated. The second system is easier to administer and is clinically more available. A patient simply is shown different-sized letters that are grayed out until they can no longer be read. This system is easier to do clinically and relates contrast sensitivity to the standard Snellen notation.

Another important measure of functional vision is how well we see in situations of glare. It is possible to have normal acuity and contrast sensitivity and to be completely blinded in the presence of any strong extraneous light source. Frequently patients have complaints of headlights obscuring their night vision. Even during the day, strong front lighting can wash out their vision. New tests have been devised that challenge acuity and contrast sensitivity in the presence of a glare source.

As we age, acuity may remain in the 20/20 range but our contrast and glare capabilities diminish. Frequently by age 70, patients' contrast has so diminished that they have difficulty driving at night. In the dark, it is hard to see on poorly illuminated roads. Tests based on contrast sensitivity may be used in the future to assess a person's visual fitness for driving.

Cataracts are a disorder of aging that can be well evaluated with the above tests. Various government reimbursement programs now require certain visual standards before they will allow ocular operations. Hence, measuring contrast and glare in addition to standard Snellen acuity is a useful adjunct in further characterizing visual loss.

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Extended-Wear Soft Contact Lenses

According to a recent Food and Drug Administration survey, nearly 20 million Americans wear contact lenses with most using soft lenses. Soft contact lenses can be used either on a daily-wear basis in which the lenses are removed and disinfected each day or on an extended-wear basis with the lenses worn overnight for a variable number of days. The most serious complication of contact lens use is bacterial corneal ulcers, which may result in corneal scarring and loss of vision requiring corneal transplantation.

Recent reports suggest that the risk of bacterial corneal ulcers is greater with the use of extended-wear than daily-wear soft contact lenses. A multicenter case-control study confirmed this observation and showed that users of extended-wear soft contact lenses who wore them overnight had a risk of bacterial corneal ulcers that was 10 to 15 times as great as that for users of daily-wear soft contact lenses.

Bacterial corneal ulcers in contact lens wearers probably require two conditions: the presence of pathogenic microorganisms that may be contaminating the eye or some aspect of the care system and a break in the corneal epithelium either from trauma or hypoxia caused by the contact lens. The use of an extended-wear soft contact lens may be associated with chronic corneal hypoxia that may disturb epithelial metabolism and result in epithelial defects through which pathogenic bacteria gain access to the corneal stroma.

Disposable soft contact lenses are extended-wear hydrogel contact lenses that are intended to be worn either six-nights-on, one-night-off and then discarded or on a daily basis and discarded every two weeks. Disposability is practical because these lenses are inexpensive.

Disposable soft contact lenses may have several advantages. First, they may reduce problems caused by noncompliance with good lens care because less lens cleaning or disinfection is required. Furthermore, the risks associated with aging lenses, such as cracks or other surface defects that might allow microbial penetration or deposits that might facilitate bacterial adherence, should be reduced. Other possible benefits include eliminating some of the allergic and toxic complications of contact lens care products. Despite all these advantages, the disposable lens has an oxygen transmissibility that is similar to other hydrogel contact lenses. In other words, this lens may be just as likely to cause chronic hypoxic stress to the cornea as other hydrogel lenses when used on an extended-wear basis. Although bacterial corneal ulcers have been associated with the use of disposable lenses, it is not known whether they are safer than other hydrogel lenses in this regard.

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Update on Retinopathy of Prematurity

Retinopathy of prematurity (ROP), previously known as retrolental fibroplasia, is a proliferative disorder of infant retinal blood vessels that can lead to blindness. While previously associated with the administration of oxygen in excess of need, the single most important factor that determines whether the condition develops under conditions of modern neonatal intensive care is the degree of an infant's prematurity. Although most cases of ROP regress spontaneously, infants with very low birth weights have a greatly increased incidence of ROP that is likely to be severe. With recent increased survival rates for infants weighing much less than 1,000 grams at birth, blindness due to ROP has become an international concern.

Retinopathy of prematurity now is classified according to an international system that allows clinical investigators to communicate better. Using that system, a multicenter clinical trial (Cryo-ROP) showed that cryotherapy administered for stage III + ROP approximately halved the rate of poor anatomic outcomes as defined by the study. In the Cryo-ROP study, only one eye of symmetrically affected infants was treated, and current recommendations generally continue this practice because of the unknown long-term fate of treated eyes.

The availability for the first time of effective treatment

of retinopathy of prematurity mandates a screening program by an interested ophthalmologist in every neonatal unit that cares for premature infants. Because the most important factor determining whether ROP will develop is birth weight, a birth weight criterion rather than an oxygen criterion appears logical, and many institutions screen all infants with birth weights of less than 1,500 grams. Because infants are highly unlikely to reach the threshold for cryotherapy before 6 weeks of age, earlier screening examinations probably are neither necessary nor warranted.

Parents of infants discovered to have threshold ROP should be offered the opportunity to have at least one eye of their baby treated with cryotherapy. Informed consent should include the warning that cryotherapy reduces but does not eliminate the risk of severe visual loss and that a complete permanent loss of vision in one or both eyes is possible despite the best available management.

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AIDS and the Management of Cytomegalovirus Retinitis

CYTOMEGALOVIRUS (CMV) RETINITIS is by far the most common vision-threatening disorder seen in patients with the acquired immunodeficiency syndrome (AIDS). Before the introduction of specific antiviral therapy against cytomegalovirus, progressive retinitis developed in these patients, terminating in blindness due to destruction of the retina. Two clinical presentations of CMV retinitis may occur—peripheral and central. Peripheral cytomegalovirus retinitis is often asymptomatic. An astute patient may notice "floaters," which represent inflammatory cells in the vitreous cavity, and also a peripheral visual field defect. It is uncommon for patients to be aware of such symptoms, however. Flashing lights may also occur as traction is placed on the retina. Peripheral disease cannot be diagnosed with the direct ophthalmoscope; visualization of the peripheral retina is best with the head-mounted binocular indirect ophthalmoscope. This examination must be done through a dilated pupil. Central CMV retinitis affects the retina closer to the optic disc and macula. This can be diagnosed by an internist or primary care provider using the direct ophthalmoscope. Dilation of the pupil is also helpful in visualizing the posterior third of the retina. Patients often will describe a visual field loss as the retina close to the central vision is affected. Visual acuity loss may also occur, either through direct involvement of the fovea (the central retina) or owing to fluid associated with adjacent CMV retinitis. In such cases, immediate therapy is required to prevent a complete loss of vision.

Patients with either peripheral or central CMV retinitis typically have systemic infection elsewhere that may be subclinical. In such patients, buffy coat cultures are often positive, indicating the systemic importance of this disease. For the past several years, many groups have had experience with the new antiviral drug, ganciclovir. These groups have shown clearly that healing of retinitis occurs during therapy with this drug. In 1989, the Food and Drug Administration approved this agent for the treatment of cytomegalovirus retinitis. Intravenous infusion of this drug prevents enlargement of the lesions within a week, and over a period of three to four weeks healing and a resolution of retinal hemorrhage and edema occur. Several groups have shown, however, that if the drug is discontinued at any time, retinitis recurs. Physicians can be misled into thinking that the retinitis is healed because clinically it does look completely inactive. The drug is virostatic, however, and it almost invariably recurs. This is important to understand because discontinuing the drug will eventually lead to loss of vision. Daily maintenance therapy with ganciclovir is required for the life of these patients. The currently recommended dose is 5 mg per kg twice a day for 10 to 14 days—the induction dose—followed by a maintenance regimen of 5 mg per kg a day 7 days a week. Drug "holidays" and poor compliance may lead to a slowly progressive retinitis that can eventually destroy the central vision.

The care of patients with cytomegalovirus retinitis must be a joint effort between an infectious disease specialist or primary care provider experienced in administering toxic antiviral drugs and an ophthalmologist trained in indirect ophthalmoscopy and retinal disease. Wide-angle fundus photographs are essential to monitor the healing of the disease, to confirm a lack of progression, and to detect early reactivation. Typically photographs are taken at the time of diagnosis and some two to four weeks later as the retina heals. Subsequent photographs can be taken at each examination or when any change is noted clinically.

With such management, recent studies show that more than 75% of patients retain excellent central visual acuity for the duration of their lives. Unfortunately, bone marrow toxicity is a major problem in patients undergoing ganciclovir therapy and may make the concurrent use of zidovudine difficult. Other drugs including foscarnet are currently being evaluated by the Studies of the Ocular Complications of AIDS group in a randomized trial sponsored by the National Eye Institute. Centers are in New York, Baltimore, Miami, New Orleans, Chicago, Dallas, San Diego, Los Angeles, and San Francisco. Such studies will determine the best antiviral drugs for treating CMV retinitis. Other recent developments include the possible use of ganciclovir in an oral form; the narrow therapeutic ratio of this drug may make such therapy difficult. Several groups are currently evaluating the use of granulocyte-monocyte colony-stimulating factor as an adjunct to ganciclovir therapy. This recombinant cytokine may be useful in treating the neutropenia that is the most common side effect of ganciclovir.

Retinal detachment is a devastating complication of CMV retinitis and often occurs in patients with healed retinitis who previously had good vision. This complication occurs in as many as 20% of patients treated for CMV retinitis, often in both eyes. Vitrectomy surgical techniques are now available that can repair these retinal detachments in most patients. The definitive procedure includes using silicone oil in many cases. The decision to do this surgical procedure will depend on the visual acuity in a patient's other eye and the potential lifespan of the patient.

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Current Recommendations for the Treatment of Diabetic Eye Disease

THE EARLY TREATMENT OF DIABETIC RETINOPATHY STUDY (ETDRS), a National Eye Institute-supported, multicenter, randomized clinical trial, has shown that photocoagulation therapy for diabetic macular edema substantially reduces the risk of loss of vision. Macular edema is a leading cause of vision loss in patients with diabetes mellitus and occurs in approximately 10% of the diabetic population. It results from fluid leakage from microaneurysms and defective retinal vessels with subsequent retinal thickening and hard exudate formation within the macula. Data from the ETDRS show that focal photocoagulation of "clinically significant" macular edema reduces the risk of vision loss by more than 50%. Laser treatment also increases the chance of visual improvement, decreases the frequency of persistent macular edema, and is not accompanied by any major adverse effects. Of note is that the benefits of treatment occur regardless of the level of visual acuity at the time of treatment. As a result, even diabetic persons with normal vision may have macular edema that should be considered for photocoagulation therapy.

The ETDRS also investigated the question of optimal timing for panretinal photocoagulation therapy. The results of the study had shown that panretinal photocoagulation substantially reduced the risk of blindness resulting from the high-risk proliferative states of diabetic retinopathy. The ETDRS results confirm that panretinal photocoagulation therapy reduces the risk of severe vision loss. In addition, investigators found that the benefits of treatment occur whether such therapy is given "early" or deferred until high-risk proliferative retinopathy occurs.

Finally, aspirin treatment was studied to determine whether it was effective in altering the course of diabetic retinopathy. The ETDRS results showed that a dose of 650 mg a day did not prevent the development of high-risk proliferative retinopathy. In addition, aspirin therapy had no effect on vision and did not increase the risk of vitreous hemorrhage.

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Using Fluorouracil in Surgical Therapy for Glaucoma

INCREASED INTRAOCULAR PRESSURE is strongly correlated with the risk of glaucomatous optic nerve damage. Current glaucoma therapy involves lowering the pressure to a level that is compatible with preserving the integrity of the optic nerve. This level may vary from patient to patient. Factors such as family history, race, myopia, and diabetes mellitus play a role in increasing the risk of damage from elevated pressures. The efficacy of therapy is determined by careful monitoring of the optic nerve appearance and by repeated measurement of the field of vision. When progressive damage continues to occur despite maximum medical therapy, a glaucoma-filtering operation may become necessary to further lower the intraocular pressure.

In glaucoma-filtering operations, a drain site connecting the anterior chamber and the episcleral space is fashioned at the junction between the cornea and sclera. This drain, which is covered by an outer coat of conjunctiva, creates a pocket or bleb into which aqueous humor flows. By directing aqueous from the inner eye into a new tissue space, the drain effects a persistent lowering of the intraocular pressure.

The average success rate of glaucoma-filtering surgical procedures in previously unoperated eyes is 75% to 85%. Although often successful initially, with time a significant number of filters fail. This occurs as a result of the normal healing response. Fibroblast proliferation at the operative site can lead to scarring, closure, and functional failure of the filter. It is thought that pharmacologic modulation of this healing response, with suppression of scarring, could improve filtering bleb survival.

Recently investigators in a large, prospective, randomized multicenter study reported a substantial improvement in the results of glaucoma filtration surgical procedures with the postoperative use of fluorouracil. All patients enrolled in the study were at a high risk for failure, having either undergone previous filtering surgical procedures or cataract extraction. The fluorouracil was injected subconjunctivally for two weeks after the filtering operation; 73% of treated versus 50% of untreated patients had successful outcomes at one year. Complications were reported but thought to be at an acceptable level.

Although earlier pilot studies showed that adjunct fluorouracil was of possible benefit in patients with a poor prognosis, clinical use has not yet been widespread. This large, well-controlled study validates the use of this agent in defined high-risk patients undergoing glaucoma filtration procedures. Through inhibition of fibroblast proliferation and scarring in the region of the surgical drain site, this therapy allows for a greater chance of continued aqueous filtration and control of intraocular pressure.

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The Dilemma of Neonatal Ophthalmic Prophylaxis

THE MOST FREQUENT CAUSE of neonatal infectious conjunctivitis today is no longer gonorrhea but chlamydia. This sexually transmitted disease caused by *Chlamydia trachomatis* is increasing rapidly in incidence (at least 3% annually) and, in addition to conjunctivitis, can cause pneumonia in infants.

While many states require silver nitrate to be the sole prophylactic antimicrobial medication, in as many as 90% of infants the medication itself induces a toxic conjunctivitis producing redness, edema, and a watery or purulent discharge. This reaction can be confused with gonococcal conjunctivitis, the very disease this agent was used to prevent.

Some states, such as California, will permit an agent other than silver nitrate to be used if it is effective. Because of the toxic conjunctivitis associated with using silver nitrate and its assumed ineffectiveness against chlamydia, many hospitals began using topical erythromycin or tetra-

cycline. Gonorrheal or chlamydial conjunctivitis has developed, however, despite the prophylactic use of these medications. In a large prospective study in Kenya comparing the use of silver nitrate with that of erythromycin, both agents were about equally effective against gonococci, *Chlamydia trachomatis,* and other forms of ophthalmia neonatorum. A larger prospective American study found that erythromycin and tetracycline ointments were just as effective for prophylaxis against gonococcal and chlamydial conjunctivitis as silver nitrate solution.

Another controversy involves the universal administration of the eyedrops. A recent study found that 80% of babies born of cesarean section within three hours of rupture of the membranes had conjunctivae that were sterile, whereas the rest bore a few cutaneous bacteria. Clearly these infants would not benefit by receiving ocular prophylaxis, as they are not exposed to the organisms of the birth canal. Infants born more than three hours after the membranes rupture may benefit from prophylaxis because they predominantly had a microaerophilic bacterial conjunctival flora similar to babies delivered vaginally.

The prevention of neonatal infectious conjunctivitis has not been totally achieved. Research needs to be conducted to better identify those newborns at risk who should receive prophylaxis and to develop better agents than those currently being used.

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Editorials

Plus Ça Change, Plus C'est la Même Chose

Readers may notice differences in the journal with the arrival of the new editor. New color, typeface, subject headings (called "ears," strangely enough) reflect certain preferences. A broadening international presence, more opportunities for young authors, poetry and art, rigorous biostatistical and epidemiologic review all signal particular interests of the editor, the Editorial Board, and, of course, the readership.

Examination of our history, philosophy, and situation leads to the following reflections, which will inevitably affect the journal as it evolves and continues its mission to serve our profession.

- Change is part of life. As opportunities, requests, and circumstances change, the journal will adjust, too, just as it has in the past. We will thrive on change, not just survive it.
- The journal is strong, sound, and forward-looking. These attributes stem from the editorial leadership of decades: Dwight Wilbur, MD (1946-1967); Malcolm S. M. Watts, MD (1968-1990), Lloyd H. Smith, Jr, MD (1968-present); and the dedication of a small but skilled professional staff. The journal relies on the support of nine western medical associations, including, most recently, the Denver Medical Society. It also relies upon the endorsement and counsel of the physicians it serves. The journal's future will depend upon the continuation of that kind of leadership, dedication, and support—as well as searches for new approaches, audiences, and backing. The journal will continue its tradition of service as it focuses on the science, public policy, public health, ethics, and humanitarian issues that affect clinical medicine. We will continue to make a difference in physicians' and patients' lives.
- Physicians are citizens, mainly good ones, with hopes and dreams, families, preferences, frustrations, satisfactions, and, for the most part, a mission to serve others.
- Excellence is necessary and achievable in research, patient care, and publication. Highest quality peer review is essential to excellence.
- Medicine is difficult. The life is hard. We need to replenish our energy and soothe our souls. We need to go beyond the bounds, the bonds of our profession to do this.
- Medicine's science and art require constant learning. To be absorbed best, science writing must be honest, accurate, fair, and clear. It is usually best when it is brief, challenging, and has a certain panache.
- History, literature, performing arts, fine arts are important to medicine because they are important to patients and to physicians. In their own way, they are as important as technology and technique. It is interesting to explore the relationships between basic and applied sciences and the humanities. DNA is poetry.
- Physicians are part of society, and, fortunately, cannot escape it. We have talents that society needs beyond patient care. We must not allow ourselves to regard offices and hospitals as refuges. When we learn of the excess mortality in Harlem or the effects of toxic wastes, we cannot keep on with practice as usual, prescribing, patching, comforting. We must participate in the solution, not only the treatment. We must work particularly hard to prevent injury and illness if we cannot fix their awful aftermath—such as first trimester rubella and nuclear war.
- As society looks abroad for ideas and information, so will we. We are part of the Pacific Rim and will increasingly exchange science and medicine with that community.
- Although individuals accomplish great things, so do groups: the householders in Le Chambon who saved Jews in Occupied France; the framers of our Constitution; the synagogues and churches that establish retirement communities and AIDS programs. I most enjoy working in concert, not solo. I admire and value the volunteers who accomplish so many tasks, including the hundreds who volunteer to write and to review papers for the journal.
- Given excellence, diversity is good. Fostering diversity is necessary. In the journal, this means covering a wide range of topics—molecular genetics to ethics to occupational medicine—and publishing authors from different locales, perspectivies, and stages in training.
- Medicine is under fire, but there is no less need for kindness and compassion, and we must strive for a constructive, rather than defensive, response. You can help to keep us informed. Send ideas and observations; send bad news . . . and good.
- Physicians rarely have enough time to do necessary work, much less to reflect upon times gone by or the significance of events or to make wise plans. We will continue the tradition of making certain your time with The Western Journal of Medicine is well spent.

LINDA HAWES CLEVER

Growing Interest in Selenium

Over the past two decades, a dramatic expansion of interest has occurred in the biomedical community concerning the trace element selenium. Although selenium was found in the 1950s to replace vitamin E in the diets of experimental animals, both the metabolic bases for its nutritional functions and its relevance in human health remained unclear until the 1970s. The first breakthrough to understanding its nutritional role came when the element was found to be an essential component of glutathione peroxidase,[1] an enzyme that metabolizes peroxides including lipid hydroperoxides. This discovery revealed that selenium is involved, in concert with vitamin E, in protecting polyunsaturated membrane lipids from oxidative degradation that would result in membrane dysfunction. The second breakthrough came when the results of studies by Chinese scientists were made known to the rest of the world, showing for the first time that a clinical disorder, Keshan disease, was associated with selenium deprivation in humans.[2] That disease, which involves a multifocal myocarditis and, frequently, periacinar pancreatic fibrosis, affects mainly children and young women in a wide region of endemic selenium deficiency in China.[3(pp347-367)] While studies have shown that Keshan disease can be prevented by prophylactic treatment with selenium, its cause remains to be fully elucidated; nevertheless, it is clear that its endemic distribution is owed to severe selenium deficiency.

With these breakthroughs came a new appreciation for this element, which had hitherto been thought of only as a factor that spared the need for vitamin E and had special importance only in veterinary applications. Consequently, research activity involving selenium increased geometrically in the 1970s and 1980s. Epidemiologic investigations indicated inverse associations of tissue selenium concentrations and risks to cancer and heart disease. Studies using

animal tumor models showed that, when administered at supranutritional levels, several selenium compounds could delay or inhibit tumorigenesis. Clinical investigations revealed very low blood selenium concentrations—approaching those of patients with Keshan disease—in patients maintained for long terms by parenteral feeding or with other highly purified nutrient solutions of low selenium content. Studies of the nutritional biochemistry of selenium have demonstrated several selenium-containing proteins—in addition to the selenium-dependent glutathione peroxidase—in animal tissues, suggesting that the element may have other as-yet-unrecognized metabolic functions.[4] Recent studies of the molecular biology of selenium have found the element to be incorporated specifically into selenocysteinyl residues of selenium-dependent glutathione peroxidase and other selenoproteins through a novel cotranslational process involving the codon UGA, which was previously thought only to signal the termination of messenger RNA synthesis.[4] Studies in China showed the quantitative relationship of selenium-dependent glutathione peroxidase activity and selenium intake in human volunteers. Gradually the body of knowledge accumulated to the point where estimates of human selenium requirements became possible.[3(pp386-388),5]

It should be noted that this expansion of interest and information came against a background of healthy skepticism on the part of many scientists and clinicians. After all, long before selenium was ever considered to be a nutrient, it had been well known for its toxic potential. In fact, the first recognition that selenium had any biologic activity came in the 1930s when it was found to be the principle toxin associated with neuropathies and dermatopathologies of grazing horses and cattle in the northern Great Plains.[6] Perhaps it is this background, as well as the continuing lack of information concerning either the metabolic basis of selenium toxicity or the quantitative toxicities of various selenium compounds, that has caused some groups to be extremely conservative in their estimations of the window of safe exposure to this element.[7(p178)]

The issue of the safe range of selenium intake is a most important one today for reasons concerning the use of selenium supplements. For example, it is now apparent that selenium supplementation is highly appropriate for total parenteral nutrition solutions and, perhaps, some low-selenium infant formulas. In addition, the voluntary use of over-the-counter selenium supplements is growing, apparently because of putative health benefits of the nutrient. Should any of the intervention studies now in progress find selenium supplementation to reduce cancer risk or to have some other health benefit, the use of over-the-counter selenium supplements can be expected to increase further. Addressing issues of the safety or toxicity of selenium involves both quantitative and qualitative considerations. One must be able to answer the compound question, "What doses of what compounds of selenium are safe?" Unfortunately, data relevant to these considerations are limited, but speculation is not.

In this issue, Fan and Kizer have reviewed information from the biomedical literature to provide background on selenium and health for those with limited direct experience in this area.[8] Their review addresses both the nutritional and toxicologic significances of selenium, with greater emphasis on the latter. This is, perhaps, not surprising for, as they acknowledge, one of the factors to have stimulated recent interest in selenium, particularly in California, is the occurrence of selenosis among waterfowl in the San Joaquin Valley drainage.[9] In fact, they present an excellent discussion of selenium intoxication effected by various means.

An anchoring concept important to that review is that any consideration of the biologic activities of selenium necessarily entails considerations of several different chemical compounds of the element. Thus, the authors' statements to the effect that "selenium can be a toxicant" must not be misread. In understanding the role of selenium in nutrition and health, it is important to keep in mind the differential metabolic use that is known to occur for the several chemical forms of selenium to which people may have exposure. All compounds of selenium are not alike in terms either of solubility, distribution in the environment, metabolism, nutritional value, or toxicity.

Another point that should be emphasized concerns the irregular geographic distribution of selenium in soils and, hence, in food chains. Severe endemic selenium deficiency is found in humans in the long mountainous belt extending from south-central to northeast China; a relatively low selenium status is found in New Zealand, Finland (before the use of selenium fertilizers), and southern and eastern China. In contrast, seleniferous conditions are found in northern Nebraska and the Dakotas, and clear selenosis has been identified in humans in three counties in central China and in parts of Colombia and Venezuela. The geographic variation in the selenium status of food chains concerns both the amounts and chemical forms of selenium distributed in the world's soils. Elemental selenium and its reduced inorganic forms (selenides) are insoluble in aqueous solvents; selenites can form stable adsorption complexes with ferric hydroxide. These forms tend not to be leached (selenates) and many organic forms (selenium analogues of methionine or cysteine) are soluble in water and tend to be well used by both plants and animals. Accordingly, the moisture level, pH, aeration, and redox conditions of soils can affect the availability to plants of the selenium contained therein. In soils that are slightly acid to neutral, selenium is present largely in organic compounds formed from the vegetation growing there; harvesting crops from such soils can deplete the soils' selenium contents. Soils that are alkaline and fairly dry can support plant selenium concentrations (predominantly as selenate) great enough to be toxic to animals. Fan and Kizer refer to some seleniferous soils; they do not point out, however, that selenium availability can vary tremendously among soils from different locations and that the total soil selenium content is a poor indicator of the availability of the element to plants and, hence, to the food chain. They correctly mention that some plant species can accumulate high tissue concentrations of selenium when grown on seleniferous soils. Such "selenium-accumulator plants"—genera *Astragalus, Machaeranthera, Haplopapus, Stanleya, Aster, Atriplex,* and others—have the metabolic facility to concentrate available soil selenium to levels approaching thousands of parts per million (dry weight basis) primarily in the form of Se-methylselenocysteine. It should also be emphasized that most plant species do not concentrate such high levels of selenium. Even when grown under seleniferous conditions, nonconcentrator species rarely accumulate more than 1 to 4 parts per million selenium, and the risk of selenosis related to their consumption must be considered low. As Fan and Kizer point out, selenosis of apparent food origin has been reported in humans only in a small number of geographically distinct, isolated locales each characterized by extraordinarily great soil concentrations of highly available forms of selenium. All other documented cases of selenosis in humans have involved the misuse of selenium-rich solu-

tions—such as gun-bluing, selenium sulfide-containing shampoos—an erroneously formulated oral supplement, or industrial exposure (primarily to selenium aerosols).

Fan and Kizer mention that, in some respects, the metabolism of selenium compounds is similar to that of their S-analogues. Selenomethionine is catabolized slowly and can be incorporated directly into proteins in lieu of methionine. Although this substitution seems to have no immediate physiologic consequence, the nonspecific incorporation of selenium into proteins by this route competes with the specific incorporation of the element into physiologically important selenium-dependent proteins. In contrast, selenocysteine appears to be catabolized rapidly to release its selenium moiety in a form (apparently a selenide) that is also produced from the oxidized inorganic selenite and selenates. The metabolic production of this common form, which appears to be a precursor to the selenocysteine found in the selenium-dependent proteins—such as glutathione peroxidase, selenoprotein "P"—means that the use of these different chemical species is similar. Thus, the nutritional activities of selenite and selenocysteine tend to be similar to and greater than that of selenomethionine. This fact is important to bear in mind, as it makes understandable the otherwise anomalous finding that two major forms of selenium in foods—selenomethionine in foods derived from plants and selenocysteine in foods derived from animals—have different metabolic fates and thus different bioavailabilities, although both may support comparable concentrations of the element in tissues.

In understanding the complexity of issues concerning the role(s) of selenium in health, it will be helpful to keep in mind a few key points. First, it is clear that selenium is an essential nutrient and that its function in the enzyme glutathione peroxidase has fundamental importance probably to all cells and, thus, to all organs in protecting against oxidative stress. This function may relate to recent findings suggestive of a protective role of selenium in cancer and cardiovascular diseases. Second, present information indicates that most American adults consume more than 55 or 70 μg selenium per day, the levels recently set as the recommended dietary allowances—for women and men, respectively.[5] In a few cases involving the use of refined liquid feeding solutions that are known to be low in selenium (total parenteral nutrition solutions), the use of selenium supplements is recommended; for healthy persons consuming mixed diets, however, selenium supplements are not likely to be beneficial. Third, though selenium compounds can be toxic, the likelihood of selenosis is only important in association with an excessive use of supplements: greater than about 500 μg total selenium per day for adults.

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Eicosanoids and Hypertension

WILSON AND CO-WORKERS elsewhere in this issue of the journal review evidence for the role of prostaglandins, particularly those in the kidney, as potentially causal, if not contributory, to systemic hypertension.[1] The authors hypothesize that the renal synthesis of thromboxane A_2 is the key prostanoid in this process. The notion is that an excess of the vasoconstricting properties of thromboxane relative to vasodilating properties of other prostanoids such as prostacyclin (prostaglandin I_2) results in increased renal vascular resistance, which in turn triggers systemic elevations of blood pressure.

The hypothesis is debatable. Cytochrome P-450-derived arachidonate metabolites may be mediators of systemic hypertension. Groups at New York Medical College (Valhalla, NY) and Vanderbilt University (Nashville, Tenn) have demonstrated the kidney's capacity to synthesize a variety of cytochrome P-450 arachidonate metabolites and have shown that these compounds have both hemodynamic and tubular effects.[2-4] Of interest is an observation that inhibiting the renal synthesis of these products in spontaneously hypertensive rats blocks the development of hypertension in this genetic model.[5] It is possible that the evidence implicating renal thromboxane—which is the genesis of the hypothesis of Wilson and associates—represents an epiphenomenon and that a different aspect of the arachidonate cascade is implicated. On the other hand, contributions may occur through both pathways or, at the extreme, there may be no role of renal or systemic eicosanoids in causing hypertension.

Wilson and colleagues cite data concerning the influence of inhibitors of thromboxane synthesis and the attendant effects on renal vascular resistance. Thromboxane synthesis inhibitors are relatively poor probes of the role of thromboxane because the blockade of thromboxane formation simply results in an accumulation of the precursor endoperoxide, which can also serve as an agonist for thromboxane receptors.[6,7] Though this endoperoxide is not as effective an agonist at vascular receptors in causing vasoconstriction as it is toward platelets in causing aggregation, it seems that a thromboxane synthesis inhibitor in itself would be unable to completely ameliorate the effects of thromboxane on vascular resistance, whether systemically or in the kidney.[7] Many investigators feel that better potential probes of thromboxane pathways (and likely better therapeutic agents) will be antagonists of thromboxane receptors.[6] A number of such antagonists have been synthesized and are undergoing trials. Their use as pharmacologic tools to address hypotheses such as that put forward by Wilson and co-workers will be of great interest.

The use of a thromboxane receptor antagonist will not be sufficient to test the hypothesis of Wilson and colleagues. If a thromboxane receptor antagonist ameliorated fixed hypertension or its development, little information would be gained as to whether this was a systemic or a renal

effect. Though it appears that the platelet thromboxane receptor may differ from that found in vascular tissue, whether or not vascular receptors in different organs also differ is less likely.[8] Thus, differentiating a systemic from a renal effect may require study designs of the use of formulations of the pharmacologic probe that allow specific targeting of the antagonist to systemic sites while excluding the kidney, and vice versa. It would seem that such study designs would be the only way to dissect the role of renal thromboxane in the hypertensive process. Luckily, with the rapid advances in this field and the intense interest of the pharmaceutical industry in the development of compounds affecting specific aspects of thromboxane's effects, it is likely that useful pharmacologic probes for dissecting thromboxane contributions to hypertension and a variety of other disorders will be available in the not-too-distant future. Such compounds might also prove to be extremely useful therapeutic agents.

Analogies to the above discussion concerning a more specific dissection of the role of renal thromboxane apply to other derivatives of arachidonate. Thus, the use of specific inhibitors of the formation of different cytochrome P-450 metabolites of arachidonic acid or antagonists of their receptors will be needed to discern their contribution to hypertension and other pathologic processes. In the future this field will evolve rapidly, will undoubtedly unravel fundamental processes of biology, and will offer important leads to the treatment of a variety of clinical conditions. Hypotheses such as that espoused by Wilson and co-workers allow a framework for the design of future probes and studies. Even if their hypothesis is disproved, its value will be in guiding appropriately designed studies. We look forward with great anticipation to future discoveries in this area.

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Alerts, Notices, and Case Reports

Lung Abscess Causing Horner's Syndrome

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WHEN FEVER, foul-smelling sputum, and a lung mass with an air-fluid level occur, the diagnosis of a lung abscess is straightforward. In the absence of typical clinical features, the diagnosis may be more difficult. The coexistence of a solid lung mass with Horner's syndrome is characteristic of a superior sulcus (Pancoast's) tumor; the presence of hoarseness strongly suggests recurrent laryngeal nerve compression due to primary or metastatic tumor. We report the case of a patient with a right lung mass, Horner's syndrome, and vocal cord paralysis due to a large lung abscess.

Report of a Case

The patient, a 67-year-old man, noted that for four weeks he had had right shoulder and neck pain, cough, and a 4.5-kg weight loss. Drooping of the right upper eyelid and hoarseness were present for three days. Hemoptysis and night sweats had occurred once but no fever. In the past the patient had had exertional angina and alcohol abuse, and he had a 60-pack-year history of cigarette smoking but no diabetes mellitus.

On physical examination he was afebrile and in no acute distress; he had right ptosis and miosis. A firm, tender mass was present in the right supraclavicular fossa and lower neck. The leukocyte count was 10.6×10^9 per liter without a leftward shift. Chest radiography (Figure 1) showed a 6-cm solid right apical-superior mediastinal mass and leftward tracheal deviation. The initial diagnostic impression was bronchogenic carcinoma with nodal metastases.

At excisional biopsy, the supraclavicular mass was necrotic and contained bloody, purulent fluid. On histologic examination there was an inflammatory response but no malignant cells. Routine culture grew coagulase-negative *Staphylococcus* organisms, but cultures for anaerobes, fungi, and mycobacteria were negative.

Four days later, hemoptysis and bleeding at the biopsy site developed. The patient was afebrile, and a computed tomographic examination of the chest (Figure 2) revealed an 8-cm superior mediastinal mass, without an air-fluid level, that extended into the apex of the right hemithorax. Paratracheal and precarinal adenopathy was present. A cytologic examination of the sputum was negative for malignant cells, and cefoxitin was administered intravenously.

On the second hospital day, fiber-optic bronchoscopy revealed paralysis of the right vocal cord. No endobronchial lesion was seen, but blood was draining from the apical and posterior segments of the right upper lobe. A transbronchial biopsy of the mass yielded tissue with many leukocytes and rare Gram-positive cocci but without evidence of malignancy. Routine cultures grew normal oral flora but were negative for mycobacteria.

The hemoptysis continued three to four times a day. The patient's temperature was 37.8°C, and on the sixth hospital day a percutaneous needle aspiration and biopsy of the mass were done. The aspirate contained many leukocytes and a few Gram-positive cocci. Routine culture grew coagulase-negative staphylococci, but cultures for mycobacteria were negative. The tissue contained an acute inflammatory response without malignant cells. On the ninth hospital day, a cardiac arrest occurred from which the patient could not be resuscitated.

At autopsy, a 15-cm abscess cavity was present in the right upper lobe that communicated with the segmental bronchus and was contiguous with the neck mass. On histologic examination there was inflammatory tissue with numerous Gram-positive cocci but no malignant cells. Mediastinal adenopathy was present and contiguous with, but not part of, the lung mass. The enlarged lymph nodes had follicular and lymphoid hyperplasia without tumor cells or bacteria.

Discussion

This patient's presentation was strongly suggestive of apical lung carcinoma with nodal metastases. Although several diagnostic studies found evidence only of infection, the many clinicians involved with this patient thought that he had lung cancer. The absence of a malignant lesion despite a thorough and careful postmortem examination of the chest was unexpected.

Lung abscesses may result from bacterial, mycobacterial, fungal, and amebic infections. Although bacterial lung abscesses may complicate the course of bacterial pneumonia or septic emboli, they may occur primarily, and a subacute course with fever, cough, hemoptysis, and weight loss is common. The aspiration of oral flora is the hypothesized mechanism of infection, and 60% of bacterial abscesses are purely anaerobic (often with more than one species) whereas 40% are mixed aerobic and anaerobic infections.[1] Although the only bacteria identified in the patient's abscess was a coagulase-negative *Staphylococcus* species, it is likely that this was merely part of a mixed bacterial infection. The hallmark of a lung abscess, a mass with an air-fluid level, is present when communication with the airway occurs but may also be seen with other conditions, including a cavitating tumor. Although the effects of compression, such as tracheal deviation and nerve palsies, have been noted in mycobacterial disease of the lung and mediastinum,[2-4] they are not associated with benign bacterial lung abscesses.

Horner's syndrome, when completely expressed, includes ptosis, miosis, and ipsilateral facial anhidrosis.[2] In the three-neuron sympathetic pathway, the first neurons originate in the hypothalamus, traverse the brain stem, and synapse with the second neurons in the lower cervical and upper thoracic spinal cord. The fibers of the second neurons leave the spinal cord through the first and second thoracic roots (T-1 and T-2), enter the sympathetic trunk, and synapse with the third neurons in the superior cervical ganglion.[5(p342)] The postganglionic fibers follow the branches of the carotid and ophthalmic arteries. Miosis is caused by decreased activity of the pupillary dilators, and ptosis

(Dugdale DC, Ritter KJ, Wilhyde DE: Lung abscess causing Horner's syndrome. West J Med 1990 Aug; 153:196-197)

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results from relaxation of the tarsal muscles. In a large series of patients with Horner's syndrome,[2] 88% of those whose cause was determined had lesions of the sympathetic trunk or the T-1 and T-2 nerve roots. Tumors caused 36% of cases, trauma caused 29%, and, in 24%, no cause was ascertained. Of the cases caused by tumors, 75% were due to malignant tumors, half of which were bronchogenic carcinomas. Compression of the T-1 and T-2 nerve roots in the brachial plexus may be associated with radicular pain, weakness, and sensory loss.[6] Of these symptoms, our patient had only shoulder pain, but the location of the mass would permit T-1 and T-2 root or sympathetic trunk compression.

This patient had hoarseness due to right vocal cord paralysis caused by compression of the right recurrent laryngeal nerve. The right recurrent laryngeal nerve turns superiorly around the right subclavian artery, but the left recurrent laryngeal nerve travels more inferiorly and turns around the aorta at the ligamentum arteriosum. Cervical, thoracic, and mediastinal lesions may compress a recurrent laryngeal nerve and cause hoarseness. Malignant neoplasms, trauma, and surgical procedures of the neck account for the majority of cases of vocal cord paralysis.[3-5] As many as 39% of cases are idiopathic, most of which resolve in six months.[7]

Figure 1.—A posteroanterior radiograph of the chest shows a right apical-superior mediastinal mass and tracheal deviation to the left.

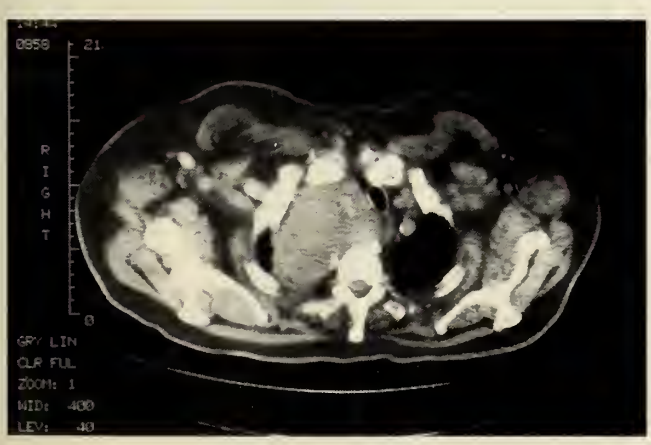

Figure 2.—A computed tomographic scan of the upper chest shows that the mass is inhomogeneous, but no air-fluid level is present.

This patient presented with clinical and radiographic abnormalities usually associated with a Pancoast's tumor. A workup did not suggest a primary lung infection. Diagnostic tests yielded either inflammatory or necrotic tissue, which was assumed to be due to a malignant tumor. The presentation of a lung abscess in this manner has not been reported, even in older series,[8,9] but must be considered during patient evaluation and treatment.

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Transient Infantile Hypertension

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THE PREVALENCE OF SYSTEMIC HYPERTENSION in childhood is estimated to range between 1% and 5% depending on the criteria used to define the disease.[1-3] Although hypertension in infants and young children is generally considered secondary, a few authors have described hypertension in infants in whom no cause could be determined (essential hypertension).[3,4] This report describes the cases of two infants in whom significant hypertension was noted incidentally before 6 months of age, and no cause was discovered. Both required antihypertensive medication for several months until their hypertension resolved.

Report of Cases

Case 1

The patient, a 35-month-old male infant, was first noted to be hypertensive at the age of 3 months. He was born prematurely, with a birth weight of 1,760 grams. A mild respiratory distress syndrome developed, but he did not require intubation or umbilical artery catheterization. Sev-

(Kuppermann N, Anand S: Transient infantile hypertension. West J Med 1990 Aug; 153:197-199)

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ABBREVIATIONS USED IN TEXT

HVA = homovanillic acid
VMA = vanillylmandelic acid

eral blood pressure readings in the neonatal intensive care unit were normal, ranging from 55 to 65 mm of mercury systolic and 30 mm of mercury diastolic. He was discharged to home at 3 weeks of age in good health. At 3 months of age, the infant was admitted to the hospital for a right inguinal herniorrhaphy, at which time his blood pressure was 135/80 mm of mercury. The hypertension was ignored, however.

At 21 months, the child was admitted to Harbor-UCLA Medical Center because of an exacerbation of his asthma, which had developed during infancy. The family history was remarkable for hypertension in the maternal and paternal grandfathers. On physical examination he had mild respiratory distress and wheezing. The blood pressure measured at the upper extremity with an 8-cm cuff and the patient supine was 140/85 mm of mercury. Growth indices were in the 20th to 50th percentile for age. The physical examination otherwise revealed no abnormalities. A urinalysis, complete blood count, serum electrolyte values, blood urea nitrogen content, and serum creatinine level were normal. A roentgenogram of the chest showed hyperinflation without cardiomegaly. An electrocardiogram revealed borderline left ventricular hypertrophy.

During his hospital stay, blood pressures ranged between 130 and 140 mm of mercury systolic and 73 and 87 mm of mercury diastolic while the patient was being treated with a regimen of parenteral theophylline and nebulized metaproterenol sulfate. Two weeks after discharge, the metaproterenol was discontinued and the patient was maintained on theophylline therapy. His hypertension persisted, however, with blood pressures in the 130 to 149/70 to 99 mm of mercury range. Thyroid function tests and urinary values of vanillylmandelic acid (VMA), homovanillic acid (HVA), and metanephrine were normal. Plasma renin and aldosterone levels were slightly increased and catecholamines were normal while on a no-added-salt diet (Table 1). An excretory urogram was normal. An ultrasonogram and magnetic resonance imaging of the abdomen revealed normal kidneys and adrenal glands. A renal arteriogram was normal; the renal vein renin values were slightly high at all sites (Table 1). No definite cause for this child's hypertension or increased renin content was found.

The patient was initially treated with hydrochlorothiazide and later other antihypertensive agents because of poor blood pressure control. During the next five months his blood pressures were 110 to 120/50 to 60 mm of mercury. Antihypertensive medications were discontinued, and subsequent blood pressures were normal. At 35 months, growth and development were normal, and his blood pressure was 108/60 mm of mercury. The plasma renin level was 1.36 ng per liter per second and aldosterone 190 pmol per liter.

Case 2

The patient, a 34-month-old male infant, was first noted to be hypertensive at 6 months of age. He was delivered at term through a cesarean section without complications. He required no resuscitation nor umbilical artery catheterization. At the age of 6 months, the infant was admitted to Charles R. Drew-Martin Luther King Jr Medical Center for decreased appetite, lethargy, sweating, and tremulousness of a few hours' duration. There was no history of any drug or poison ingestion. A family history was remarkable only for untreated hypertension in the maternal grandmother. On physicial examination the agitated infant had a heart rate of 144 beats per minute, a respiratory rate of 48, and a blood pressure of 130/70 mm of mercury taken with a 6-cm cuff in the right arm with the patient in the supine position. Growth indices and the findings of the rest of the physical examination were normal. A urinalysis, complete blood count, serum electrolyte levels, blood urea nitrogen content, and serum creatinine level were normal. Urine toxicology was negative for cocaine and phencyclidine.

Over the initial several hours, the infant's systolic blood pressure varied between 120 and 150 mm of mercury and diastolic blood pressure between 70 and 90 mm of mercury. He was treated with hydralazine hydrochloride, but his blood pressure remained intermittently elevated. Propranolol hydrochloride was added to the treatment regimen. An excretory urogram, an ultrasonogram of the abdomen, and a computed tomographic scan of the head (obtained because of initial jitteriness) were normal. Thyroid function tests, urinary values of VMA and HVA, and plasma aldosterone

TABLE 1.—*Laboratory Evaluation of Renin, Aldosterone, and Catecholamine Levels in Infants With Essential Hypertension**

Serum Laboratory Test	*Serum Values†*	
	Patient 1	*Patient 2*
Aldosterone, pmol/liter	340 (140-1,700)	220 (30-4,400)
Renin, ng/liter • s		
Peripheral	4.9 (<2.78)‡	5.81 (<2.78)§
		4.22§‖
Central	† ‖	
Inferior vena cava, above renal arteries	3.44 (<2.78)	
Inferior vena cava, below renal arteries	3.17 (<2.78)	
Right renal vein	3.56 (<2.78)	
Left renal vein	3.94 (<2.78)	
Total catecholamines, pmol/liter	3,248	10,290
Epinephrine, pmol/liter	482 (<382)	1,480 (<382)
Norepinephrine, pmol/liter	2,648 (591-2,364)	8,392 (591-2,364)
Dopamine, pmol/liter	118 (<196)	418 (<196)

*Serum specimens were taken with patient in a supine position.
†Numbers in parentheses represent normal values.
‡Patient taking theophylline.
§Patient taking hydralazine hydrochloride.
‖Patient taking propranolol hydrochloride.

levels were normal. Plasma renin and catecholamine levels were slightly elevated (Table 1).

During the next few months, his blood pressures ranged from 80 to 100/40 to 70 mm of mercury while on a regimen of hydralazine and propranolol. Both medicines were gradually reduced in dosage, but this was associated with a rise in the blood pressure, requiring an increase in the antihypertensive medication dosage. Renal angiography was repeatedly cancelled because of intercurrent colds and ear infections. At 13 months of age, the blood pressure was 80/60 mm of mercury while the infant was receiving hydralazine and propranolol. Subsequently both medications were tapered and discontinued by 16 months. At 17 months of age, the blood pressure was 100/50 mm of mercury and a peripheral renin value was 0.42 ng per liter per second. His blood pressure remained normal over the following 17 months. At 34 months of age, the patient's blood pressure was 90/60 mm of mercury and growth and development were normal.

Discussion

Hypertension in infants and young children is generally considered secondary.[3] Recently, however, a few authors have described essential hypertension in newborns and infants.[3,4] Little is known about the incidence and natural history of essential hypertension in this age range. Essential hypertension in infants must remain a diagnosis of exclusion, after other disorders have been excluded by a thorough investigation.

The common secondary causes of hypertension in newborns and infants are renal artery thrombosis following umbilical artery catheterization, coarctation of the aorta, renal artery stenosis, and other renal or endocrinologic abnormalities.[3] All of these disorders, and other known causes of hypertension, were excluded in our patients by history, appropriate investigation, and clinical course. The cause of their hypertension could not be determined. Although serum catecholamine levels were mildly elevated in our second patient, urinary HVA and VMA values were normal, and the clinical course was not felt to be consistent with neuroblastoma or pheochromocytoma. Both of the patients had slightly elevated renin values early in their illnesses, which may have reflected a stress response or a transient renal or renovascular insult. Perhaps low-salt intake in the first patient contributed to the elevated serum renin level, but a 24-hour urine specimen was not collected for correlating sodium with renin content. Some authors suggest that administering theophylline may raise the blood pressure, but others have shown that if there is any increase in the blood pressure, it is mild.[5] In addition, the first patient's blood pressure became normal while he continued taking theophylline.

Until the early 1970s it was generally thought that hypertension in children was persistent, unless surgically correctable, and carried a poor prognosis.[6,7] Recently a few studies suggest that hypertension detected in infancy or childhood may resolve with medical treatment and later blood pressures remain normal without any medication.[3,8] In contrast to our patients, most in those studies had hypertension due to renovascular or renal parenchymal disease, and the hypertension usually persisted for considerably longer periods than it did in our patients. We elected to treat our patients' hypertension because patient 1 had left ventricular hypertrophy on an electrocardiogram and patient 2 had symptoms of agitation, although it is possible that the blood pressures would have reverted to normal in both patients without any treatment.

In summary, the two cases presented in this report demonstrate that significant essential hypertension may occur in infants and can resolve within months. Therefore, hypertensive infants who initially require medication to control their blood pressure should be evaluated frequently and have trials of reduced medicine dosage to avoid prolonged and unnecessary treatment of a normal blood pressure.

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Valproic Acid-Associated Encephalopathy

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Most reports of valproic acid (VPA)-associated encephalopathy have been of cases in the pediatric population. In most of these patients, the serum ammonia concentration was elevated, and VPA was used in combination with other antiepileptic drugs. We report the case of a woman with VPA-associated encephalopathy to emphasize this as a possible diagnosis in adults and to consider the possibility that this may be an underreported side effect to which physicians should be alert.

Report of a Case

The patient, a 59-year-old woman with a seizure disorder since age 38, was transferred from a community hospital because of prolonged confusion after a generalized seizure. Her seizures had been well controlled with the use of phenytoin, as she reportedly had only four "spells" in the previous 20 years. According to witness accounts, each seizure was similar: without warning, the patient would lose consciousness and show "stiffness and shaking of all extremities," which lasted a minute or less, but there was no incontinence. The patient was confused for about two hours after the event. She had had no history of head trauma, and in 1981 a computed tomographic scan of the

(Jones GL, Matsuo F, Baringer JR, et al: Valproic acid-associated encephalopathy. West J Med 1990 Aug; 153:199-202)

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ABBREVIATIONS USED IN TEXT

CPS = carbamoyl-phosphate synthetase
EEG = electroencephalogram
VPA = valproic acid

head was normal. Nevertheless, electroencephalograms (EEGs) in 1969, 1970, and 1981 showed 3-Hz spike-and-wave or polyspike-and-wave activity with sleep.

In the two months before admission to the referring hospital, the patient was admitted at least twice to yet another community hospital where she was considered to be in a "nonconvulsive status," both on clinical grounds and by EEG. She was treated on each occasion with the intravenous administration of diazepam, and on the second admission phenobarbital was added to her existing phenytoin regimen. A subsequent neurologic evaluation by one of us (W.H.R.) suggested a diagnosis of primary generalized epilepsy with an atypical spike-and-wave EEG pattern. A regimen of VPA (divalproex sodium) was started, and a phenobarbital taper was begun. Four days later she had a witnessed generalized tonic-clonic seizure at home and was admitted to the referring hospital. On admission, drug concentrations were 10.2, 16.4, and 43.9 μg per ml for phenytoin, phenobarbital, and VPA, respectively. The phenobarbital taper was continued, while VPA and phenytoin dosages were increased. Although she regained consciousness, her postictal recovery was protracted. On the third hospital day the patient again had a witnessed generalized tonic-clonic seizure even though blood phenytoin and VPA concentrations were in the therapeutic ranges. Because she remained encephalopathic several hours after the latest seizure, she was transferred to the University of Utah Medical Center.

The patient's medical history was notable only for her seizure disorder; the family history was noncontributory. Medications on transfer included phenytoin (Dilantin), 100 mg intravenously every six hours; phenobarbital, 60 mg per nasogastric tube every eight hours; and divalproex (Depakote), 500 mg per nasogastric tube every eight hours.

A neurologic examination was remarkable for stupor. The patient occasionally moved all extremities spontaneously and reproducibly to pain. She did not respond to visual threat and had roving eye movements. Her fundi were normal, pupils were reactive to light, and there was no evidence of other cranial nerve deficits. Deep tendon reflexes were 1+ to 3+ and were symmetric. Bilateral Babinski's signs were present.

The major differential diagnosis established on admission included both petit mal (absence) status and metabolic encephalopathy. Because her recent history was suggestive of primary generalized epilepsy, petit mal stupor was strongly considered. A plasma ammonia level measured on admission, however, was elevated at 116 μmol per liter (normal 7 to 27). The remainder of the chemistry profile was normal except for the γ-glutamyl transferase level, which was elevated at 183 units per liter (normal 0 to 33). Her cerebrospinal fluid was normal, as was the rest of her laboratory evaluation. Both VPA and phenobarbital were discontinued, and lactulose was given by nasogastric tube. An EEG showed a mixture of diffuse slowing, 2- to 3-Hz spike-and-wave activity, and polyphasic sharp transients. An early subsequent plasma ammonia level measured more than 300 μmol per liter, but during the next two days her mental state improved remarkably as her plasma ammonia level decreased to normal (22 μmol per liter on day of discharge). Subsequent EEGs showed a return to normal.

Discussion

Valproic acid has become widely used in treating generalized seizure disorders. The most common toxic effects are gastrointestinal, including anorexia, nausea, and vomiting, but these are transient and can usually be controlled by adjusting the dosage or by making sure the drug is taken with food.[1] Other gastrointestinal toxic effects include an asymptomatic increase in liver enzyme activities, which return to normal after discontinuing the drug.[2] Of greater significance is the hepatic failure[3,4] and Reye's syndrome-like symptoms[5,6] that have been associated with VPA use, particularly when combined with other antiepileptic drugs in infants or young children. There are, however, recent reports of hepatic failure in older children receiving monotherapy.[7,8]

Nervous system toxicity has been documented in numerous reports since 1973 and includes a spectrum of symptoms from drowsiness to stupor and coma. Early discussions focused on possible metabolic or epileptogenic actions of VPA to account for the encephalopathy. It is not the result of hepatocellular toxicity, as stupor and coma occur independently of abnormal increases in liver enzyme levels or the clinical syndrome associated with hepatic failure.[9] When VPA use was found to be associated with an increased serum ammonia concentration, much discussion centered on the relationship between the hyperammonemia and encephalopathy. The hyperammonemia, like the encephalopathy, occurs in the absence of other indices of hepatic failure.

In 1979 Sackellares and colleagues reported the cases of two adults and two children in whom confusion, stupor, or coma occurred within hours to weeks after VPA was added to a regimen that included at least two other antiepileptic agents.[10] In each patient the EEG was similar, revealing generalized, rhythmic, high-amplitude, bisynchronous 1.5- to 3-Hz delta activity, along with bursts of spikes and waves. Intravenous diazepam was given because continued seizure activity was suspected, but there was further slowing of the EEG activity and clinical worsening. Each patient became fully alert within a few days after VPA therapy was discontinued. The authors thought it unlikely that the symptoms were caused by metabolic disturbances because routine serum chemistry results were normal. Sackellares and co-workers considered the possibility of an epileptogenic effect but concluded that because of the clinical and EEG worsening induced by diazepam, this was not likely. These authors did not measure serum ammonia concentrations. One of the earliest reports of VPA-associated hyperammonemia appeared in 1980 when Coulter and Allen described the case of a young girl who became lethargic while receiving VPA and who was noted to have a mildly elevated serum ammonia level.[11] Also, Sills and associates reported a case of pronounced hyperammonemia in a patient who had been receiving VPA for a long time.[12] In 1981 Ruwat and colleagues described a prolonged generalized seizure and persistent lethargy in an 11-year-old girl two days after VPA was added to a regimen of clonazepam and ethosuximide.[13] Although routine serum chemistry results—including a liver profile—were normal, serum ammonia levels rose as high as 126 μmol per liter (normal 11 to 28), requiring the discontinuation of VPA.

Numerous additional studies have since appeared documenting the association of VPA therapy with hyperammonemia and sometimes encephalopathy.[14-27] Most are in children and show EEG abnormalities similar to those discussed earlier, especially when hyperammonemia is substantial. Not all studies showed hyperammonemia with

VPA monotherapy,[21,23] although all studies reported its occurrence in patients treated concomitantly with other antiepileptic drugs. In one study the mean plasma ammonia concentration in patients receiving antiepileptic agents other than VPA was 25 μmol per liter (normal range 10 to 30); the mean value in patients receiving VPA with other antiepileptic drugs was 46 μmol per liter, but levels as high as 140 μmol per liter were seen.[15]

Based on these studies, several general statements can be made regarding the role of VPA in hyperammonemia and encephalopathy. With and without encephalopathy, hyperammonemia is being increasingly documented in both adults and children. There is little doubt that VPA, even in monotherapy and with drug concentrations in the reference range, produces abnormal elevations of serum ammonia. Such elevations occur in the absence of other indices of hepatic dysfunction, such as elevated aminotransferase levels. Symptoms typically occur soon—within days—after starting VPA therapy, and they resolve promptly after its discontinuation. While the dependence of serum ammonia levels on VPA concentrations is uncertain (it appears to have little dose dependence), it is clear that other antiepileptic drugs may potentiate the VPA effect. The relative potency of the common antiepileptic agents in potentiating the VPA-associated hyperammonemia remains unclear, but phenytoin, phenobarbital, and carbamazepine are all effective. Also evident is that there is little correlation of the serum ammonia concentration with the encephalopathy associated with VPA therapy, and this has led some to refute the causal role of ammonia in such encephalopathy. In any case, the prompt discontinuation of VPA is uniformly associated with a remission of symptoms, an abatement of EEG abnormalities, and a reduction of serum ammonia levels.

Considerable speculation has taken place regarding possible mechanisms of VPA-induced hyperammonemia. The structure of VPA and its metabolites has been compared with that of certain pentaenoic acid derivatives, which are short-chain fatty acids known to uncouple mitochondrial oxidative phosphorylation.[27] Based on the effects of these and other short-chain fatty acids in rodents, some authors have speculated that VPA or its metabolites might act by inhibiting the activity of ornithine carbamoyltransferase and carbamoyl-phosphate synthetase (CPS), or the activator of CPS, *N*-acetylglutamate.[28] In rodents, VPA has been shown to directly inhibit baseline and activated hepatic mitochondrial CPS activity.[29] Indeed, patients with a partial deficiency of CPS appear more susceptible to VPA, and overt cerebral edema associated with hyperammonemia has been documented in such patients treated with VPA.[9,30] Other evidence of mitochondrial dysfunction induced by VPA includes increased alanine, lactate, pyruvate, glycine, and serine concentrations and decreased aspartate, glutamate, glutamine, free coenzyme A, and acetyl-CoA concentrations.[29,31] Thus, although the mechanism of the VPA-induced hyperammonemia remains unclear, it may be due to the depletion of mitochondrial acetyl-CoA and decreased production of *N*-acetylglutamate, the obligatory activator of the first enzyme of the urea cycle, CPS.

The case we present herein typifies the relatively rapid occurrence—four days in this patient—of encephalopathy after the initiation of VPA therapy and likewise the relatively rapid resolution—two days—after the discontinuation of VPA. Although lactulose was administered to our patient, this may in retrospect have been unnecessary. A particularly intriguing question is the possible contribution of seizure activity to the encephalopathy in our patient and others. In rare instances, VPA has been reported to exacerbate seizures or increase epileptogenic activity,[32] and we have just documented fully the speculations about the role of seizures in VPA-associated encephalopathy. Little attention has been given, though, to the possible effect of hyperammonemia in lowering the seizure threshold. It is known that ammonia is preferentially detoxified in the brain to glutamine and therefore depletes the available glutamic acid. Because glutamic acid is a precursor of γ-aminobutyric acid, the major mediator of central inhibition, notable elevations of serum (and brain) ammonia levels may thus lower the seizure threshhold and thereby provide a "metabolic" explanation for at least some of the EEG abnormalities and mental state changes seen in VPA-associated encephalopathy.

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Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, mouse lymphoma assay, chromosome aberration tests, and a micronucleus test.

In a two-generation, perinatal and postnatal fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

Pregnancy—Teratogenic Effects—Pregnancy Category C—Oral reproduction studies in rats at doses up to 300 times the human dose and in Dutch Belted rabbits at doses up to 55 times the human dose revealed no evidence of impaired fertility or teratogenic effect, but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights. On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in one fetus, and at 50 mg/kg, it produced ventricular anomaly, distended abdomen, spina bifida, hydrocephaly, and enlarged heart in one fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers—Studies in lactating women have shown that 0.1% of an oral dose is secreted in human milk in proportion to plasma concentrations. Because of growth depression in pups reared by treated lactating rats, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

Pediatric Use—Safety and effectiveness in children have not been established.

Use in Elderly Patients—Healing rates in elderly patients were similar to those in younger age groups as were the rates of adverse events and laboratory test abnormalities. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

Adverse Reactions: Clinical trials of varying durations included almost 5,000 patients. Among the more common adverse events in domestic placebo-controlled trials of over 1,900 nizatidine patients and over 1,300 on placebo, sweating (1% vs 0.2%), urticaria (0.5% vs <0.01%), and somnolence (2.4% vs 1.3%) were significantly more common with nizatidine. It was not possible to determine whether a variety of less common events was due to the drug.

Hepatic—Hepatocellular injury (elevated liver enzyme tests or alkaline phosphatase) possibly or probably related to nizatidine occurred in some patients. In some cases, there was marked elevation (>500 IU/L) in SGOT or SGPT and, in a single instance, SGPT was >2,000 IU/L. The incidence of elevated liver enzymes overall and elevations of up to three times the upper limit of normal, however, did not significantly differ from that in placebo patients. Hepatitis and jaundice have been reported. All abnormalities were reversible after discontinuation of Axid.

Cardiovascular—In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in two individuals administered Axid and in three untreated subjects.

CNS—Rare cases of reversible mental confusion have been reported.

Endocrine—Clinical pharmacology studies and controlled clinical trials showed no evidence of antiandrogenic activity due to nizatidine. Impotence and decreased libido were reported with equal frequency by patients on nizatidine and those on placebo. Gynecomastia has been reported rarely.

Hematologic—Fatal thrombocytopenia was reported in a patient treated with nizatidine and another H_2-receptor antagonist. This patient had previously experienced thrombocytopenia while taking other drugs. Rare cases of thrombocytopenic purpura have been reported.

Integumental—Sweating and urticaria were reported significantly more frequently in nizatidine- than in placebo-treated patients. Rash and exfoliative dermatitis were also reported.

Hypersensitivity—As with other H_2-receptor antagonists, rare cases of anaphylaxis following nizatidine administration have been reported. Because cross-sensitivity among this class has been observed, H_2-receptor antagonists should not be administered to those with a history of hypersensitivity to these agents. Rare episodes of hypersensitivity reactions (eg, bronchospasm, laryngeal edema, rash, and eosinophilia) have been reported.

Other—Hyperuricemia unassociated with gout or nephrolithiasis was reported. Eosinophilia, fever, and nausea related to nizatidine have been reported.

Overdosage: Overdoses of Axid have been reported rarely. If overdosage occurs, activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. Renal dialysis for four to six hours increased plasma clearance by approximately 84%.

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(Continued from Page 128)

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December 10-14—**Emergency Medicine Symposium II: Trauma and Surgery.** UCSD at La Jolla Marriott. Mon-Fri. 32 hrs. $485. Contact: UCSD.

January 14-18—**Emergency Medicine Symposium I: Cardiology, Pulmonary, Neurology.** UCSD at Hyatt Regency, La Jolla. 32 hrs. $485. Contact: UCSD.

FAMILY PRACTICE/PRIMARY CARE

August 24-26—**3rd Coronado Summer Conference on Primary Care Medicine: A Practical Approach.** Scripps Clinic and Research Foundation at Le Meridien Hotel Coronado Island, San Diego. Fri-Sun. 15 hrs. $275. Contact: Heidi Jurgens, Box 400S, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

October 3-5—**Primary Care Medicine: Principles and Practice.** UCSF at Holiday Inn Golden Gateway, San Francisco. Wed-Fri. 19 hrs. $425. Contact: UCSF.

INTERNAL MEDICINE

August 19-24—**New Advances in Internal Medicine.** UCD at Hyatt Regency, Monterey. Sun-Fri. 23 hrs. $450. Contact: UCD.

September 13-15—**3rd Annual New Advances in Common Neurologic Disorders.** UCSD at Catamaran Resort Hotel, San Diego. Thurs-Sat. 14 hrs. $300. Contact: Meeting Management, 5665 Oberlin Dr, Ste 110, San Diego 92121. (619) 453-6222.

September 14-16—**Gastroenterology.** UCSF at San Francisco Hilton and Towers. Fri-Sun. 17 hrs. $415. Contact: UCSF.

October 18-20—**Breast Cancer Seminar.** Memorial/UCI Center for Health Education at Stouffer Hotel, Palm Springs. Thurs-Sat. Contact: UCI.

October 22-24—**14th Annual Cancer Symposium.** Scripps Memorial Hospital at Sheraton Harbor Island Hotel, San Diego. Mon-Wed. 20 hrs. $390. Contact: Meeting Management, 5665 Oberlin Dr, Ste 110, San Diego 92121. (619) 453-6222.

October 20—**Lipids Conference.** UCD at Sheraton Sunrise, Sacramento. Sat. Contact: UCD.

November 9-10—**Metabolic Control of Diabetes.** Memorial/UCI Center for Health Education at Westin South Coast Plaza, Costa Mesa. Fri-Sat. Contact: UCI.

November 30-December 1—**Northern California Internal Medicine Update.** UCD at Hilton Inn. Fri-Sat. Contact: UCD.

December 6-9—**Fall Symposium on Back Pain.** American Back Society at San Francisco Marriott Hotel. Thurs-Sun. 18 hrs. Contact: Aubrey Swartz, MD, ABS, 2647 E 14th St, Ste 401, Oakland 94601. (415) 536-9929.

OB/GYN

August 17-19—**3rd Annual Perinatal Review.** Memorial/UCI Center for Health Education at Four Seasons Hotel, Newport Beach. Fri-Sun. Contact: UCI.

August 21-25—**8th Annual Controversies in OB/GYN.** Memorial/UCI Center for Health Education at Mauna Kea, Hawaii. Tues-Sat. Contact: UCI.

November 8-11—**Current Issues in Perinatal Medicine.** Memorial/UCI Center for Health Education at Marriott's Rancho Las Palmas Resort, Palm Springs. Thurs-Sun. Contact: UCI.

November 11-17—**13th Annual Review Course in Clinical OB/GYN and/or Gynecological Histopathology.** Memorial/UCI Center for Health Education at Westin South Coast Plaza, Costa Mesa. 1 week. Contact: UCI.

November 29-December 1—**Nebraska OB/GYN Society Meeting.** Nebraska OB/GYN at Las Vegas, Nevada. Thurs-Sat. Contact: University of Nebraska Medical Center, 42nd and Dewey Ave, Omaha, NE 68105-1065. (402) 559-4152.

OCCUPATIONAL AND ENVIRONMENTAL MEDICINE

October 2-7—**Sports Medicine Update.** Memorial/UCI Center for Health Education at Mauna Kea Hotel, Hawaii. Tues-Sun. Contact: UCI.

October 8-19—**Occupational and Environmental Medicine Session II.** UCSF at Cathedral Hill Hotel, San Francisco. 1½ weeks. 80 hours. $1,200. Contact: UCSF.

October 15-19—**Current Topics in Occupational Medicine.** UCSF at Cathedral Hill Hotel, San Francisco. Mon-Fri. 40 hrs. $600. Contact: UCSF.

OPHTHALMOLOGY

August 26-30—**Ophthalmology Update: 1990.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Thurs. Contact: UCD.

August 26-29—**External Disease: Diagnosis and Management for the 1990s.** UCD at Hyatt Regency Lake Tahoe, Incline Village, Nevada. Sun-Wed. 13 hrs. $350. Contact: UCD.

September 14-16—**Uveitis/Retinal Frontiers: Diagnostic, Medical and Surgical Approaches to Uveitis.** UCSF at Carmel Valley Ranch Resort. Wed-Fri. 12 hrs. $395. Contact: UCSF.

September 17-18—**Blepharoplasty Workshop: Principles and Technique.** UCSF at Portman and Chancellor Hotels, San Francisco. Mon-Tues. 11 hrs. $690. Contact: UCSF.

November 30-December 2—**American Academy of Ophthalmology Regional Update Course.** American Academy of Ophthalmology at Los Angeles. Fri-Sun. Contact: Gary Holland, (213) 825-9508.

December 13-14—**New Ideas on Common Retinal Disorders.** UCSF at Grand Hyatt Union Square, San Francisco. Thurs-Fri. Contact: UCSF.

ORTHOPAEDICS

October 4-6—**Orthopaedic Update.** UCSD at Hyatt La Jolla. Thurs-Sat. Contact: Pat Curl, PO Box 33185, San Diego 92103. (619) 692-9115.

PATHOLOGY

October 4-6—**International Symposium on Medical Virology.** UCI at Four Seasons Hotel, Newport Beach. Thurs-Sat. Contact: Luis M. de la Maza, (714) 634-6868.

(Continued on Page 205)

CONTINUING MEDICAL EDUCATION

(Continued from Page 204)

October 12-14—**8th Postgraduate Course in Medical Mycology (Dermatomycology).** UCSF. Fri-Sun. 16 hrs. Contact: UCSF.

October 19—**Fine Needle Aspiration Tutorials.** UCSF. Fri. 7 hrs. Contact: UCSF.

October 20—**30th Annual Scientific Symposium on Kidney Disease.** National Kidney Foundation of Southern California at Wyndham Palm Springs. Sat. Contact: Sylvie Tarro, 5777 W Century Blvd, Ste 395, Los Angeles 90045. (213) 641-8152.

November 2-3—**Update on Thyroid Disease—1990.** UCSF at Hyatt Regency Embarcadero, San Francisco. Fri-Sat. 12 hrs. $150. Contact: UCSF.

November 10—**Infectious Diseases in Critical Care.** UCD at Hilton Inn, Sacramento. Sat. Contact: UCD.

PEDIATRICS

September 7-8—**Pediatrics and Environmental Health: The Pediatrician as Investigator, Educator, and Advocate.** Children's Hospital Oakland at Berkeley Conference Center. Fri-Sat. 12 hrs. $85. Contact: Joy Carlson, EPI Training Project, 5900 Hollis St, No. E, Emeryville 94608. (415) 540-3657.

October 7-14—**15th Annual Pediatrics for the Practitioner.** Memorial/UCI Center for Health Education at Mauna Kea Hotel, Hawaii. 1 week. Contact: UCI.

October 18-21—**47th Annual Brennemann Memorial Lectures.** Los Angeles Pediatric Society at San Diego Marriott-La Jolla Hotel, La Jolla. Thurs-Sun. 15 hrs. $325. Contact: LAPS, (213) 757-1198.

November 9-11—**Infectious Diseases in Children.** Children's Hospital Oakland at Monterey Plaza Hotel on Cannery Row. Fri-Sun. 12 hrs. $280. Contact: Kim Leadon, 747 52nd St, Oakland 94609. (415) 428-3021.

December 1—**8th Annual Binational Pediatric Conference.** Children's Hospital San Diego at Mercy Hospital Education Center, San Diego. Sat. 5 hrs. Contact: CME Dept, Children's Hospital, (619) 576-4072.

December 8-9-**Stabilization and Management of the Critically Ill Child.** UCSF at Hyatt Regency Hotel, San Francisco. Sat-Sun. 9 hrs. Contact: UCSF.

January 23-26—**Health Science Response to Child Maltreatment 1991.** Children's Hospital San Diego at U S Grant Hotel, San Diego. Wed-Sat. 22 hrs. Contact: Children's Hospital, (619) 576-5814.

PSYCHIATRY

October 11-12-**No Crystal Stair: Models for Successful Development of Afro-Americans.** UCSF at Laurel Heights Campus, San Francisco. Thurs-Fri. Contact: UCSF.

October 19-21—**Creating an Integrated Psychiatry: Challenge of the 90's.** California Psychiatric Association at Claremont Hotel, Berkeley. Fri-Sun. 11 hrs. Contact: Barbara Gard, 1100 N St, Ste 2-E, Sacramento 95814. (916) 442-5196.

October 26-27—**The Aftermath of Suicide: Counseling Survivors.** UCSF on Campus. Fri-Sat. $190. Contact: UCSF.

November 9-11—**36th Annual Group Therapy Symposium.** UCSF at Sir Francis Drake Hotel, San Francisco. Fri-Sun. Contact: UCSF.

November 12-16—**Introduction to Medical Hypnosis.** UCSD at Inn at Del Mar. Mon-Fri. Contact: UCSD.

RADIOLOGY

August 17-19—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton Resort Hotel, Laguna Niguel. Fri-Sun. 18 hrs. $400. Contact: UCSD.

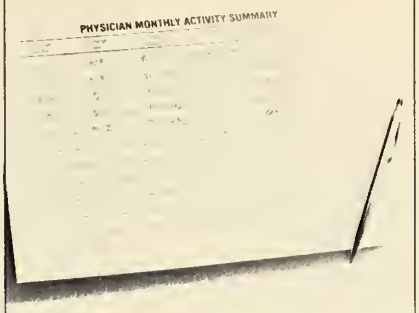
August 18-19—**Intravascular Ultrasound Imaging.** Memorial/UCI Center for Health Education at Anaheim Hilton Hotel. Sat-Sun. Contact: UCI.

August 23-28—**6th Annual Physics and Biology of Radiology.** UCSD at Hanalei Hotel, San Diego. Thurs-Tues. 25 hrs. $395. Contact: UCSD.

September 6-8—**6th Annual Sonography Update Conference and Exhibit.** UCSD at Hotel del Coronado, San Diego. Thurs-Sat. 18 hrs. $395. Contact: UCSD.

September 7-10—**6th Annual Sonography Update for Physicians and Sonographers.** UCSD at Hotel del Coronado, San Diego. Fri-Mon. 18 hrs. $375. Contact: UCSD.

(Continued on Page 206)



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September 8-9—**Sonography Registry Review.** UCSD at Hotel del Coronado, San Diego. Sat-Sun. 16 hrs. $200. Contact: UCSD.

October 6-7—**Ultrasound: 1990**. UCD at Red Lion Inn, Sacramento. Sat-Sun. 10 hrs. $195. Contact: UCD.

October 20-21—**Advanced Imaging of the Musculoskeletal System.** UCSD at Hotel del Coronado. Sat-Sun. 12 hrs. $125. Contact: UCSD.

October 22-26—**15th Annual San Diego Postgraduate Course.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 27 hrs. $300. Contact: UCSD.

October 26-28—**10th Annual Interventional Radiology.** UCSD at Hotel del Coronado, San Diego. Fri-Sun. 18 hrs. $350. Contact: UCSD.

November 9-11—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton Resort Hotel, Laguna Niguel. Fri-Sun. 20 hrs. $400. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

December 7-9—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton Resort Hotel, Laguna Niguel. Fri-Sun. 18 hrs. $400. Contact: UCSD.

January 19-21—**Advanced Seminars in Diagnostic Imaging.** UCSF at Ritz-Carlton Resort Hotel, Laguna Niguel. Sat-Mon. 20 hrs. $400. Contact: UCSF.

SURGERY

September 1990-December 1990—**Temporal Bone Surgical Dissection Courses: 1990.** House Ear Institute, 5 days per month. 53 hrs. $975. Contact: Antonio de la Cruz, MD, Director of Education, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

October 6-8—**Anatomic Basis for Aesthetic Surgery: Hands-On Laboratory Course.** UCD at Hyatt Regency, Davis. Sat-Mon. Contact: UCD.

November 8-10—**Otolargyngology Update: 1990.** UCSF at Union Square Holiday Inn, San Francisco. Thurs.-Sat. 18 hrs. $375. Contact: UCSF.

January 18-19-**What's New in General Surgery: 13th Annual Postgraduate Course.** UCD at Capitol Plaza Holiday Inn, Sacramento. Fri-Sat. Contact: UCD.

OF INTEREST TO ALL PHYSICIANS

September 10-14—**Hyperbaric Medicine.** UCI/Memorial Medical Center at Long Beach. Mon-Fri. 30 hrs. $650. Contact: Celia Loney, 2801 Atlantic Ave, PO Box 1428, Long Beach 90891. (213) 595-2000.

September 14-16—**Annual Conference on Pain Management.** American Academy of Pain Management at University of the Pacific, Stockton. Fri-Sun. 11 hrs. $235. Contact: Institute of Pain Management, 1917 Memorial Dr, Ste A-1, Ceres 95307. (209) 538-4942.

November 9-10—**2nd Annual Symposium—Diagnosis and Treatment of Bone and Soft Tissue Tumors: A Multidisciplinary Approach.** UCD at Hyatt Regency, Sacramento. Fri-Sat. 14 hrs. $345. Contact: UCD.

November 12-16—**Hyperbaric Medicine.** UCI/Memorial Medical Center at Long Beach. Mon-Fri. 30 hrs. $650. Contact: Celia Loney, 2801 Atlantic Ave, PO Box 1428, Long Beach 90801. (213) 595-2000.

December 6—**Common Musculoskeletal Problems—Foot and Ankle.** VA Medical Center Sepulveda. Thurs. 5 hrs. Contact: Arun Mehta, MD, Rehabilitation Medicine Service (117), VAMC Sepulveda 91343. (818) 895-9344.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

August 20-24—**Annual Internal Medicine Board Review.** U of Colo, Denver. Mon-Fri. Contact: U of Colo.

September 4, 11, 18—**OB Nursing in the 1990s.** The Children's Hospital at University Hospital, Denver. Tues. Contact: Trish Beachy, (303) 270-8376.

September 6—**Rocky Mountain Hand Surgery Society.** Adirondacks Restaurant, Denver. Thurs. Contact: Carol Goddard, (303) 770-6048.

September 10-14—**Family Practice Review.** U of Colo, Denver. Mon-Fri. Contact: U of Colo.

September 20—**Colorado Radiological Society.** Hyatt Regency DTC, Denver. Thurs. Contact: Carol Goddard, (303) 770-6048.

September 20—**Colorado Society of Clinical Pathologists.** Denver, location to be announced. Thurs. Contact: Carol Goddard, (303) 770-6048.

September 21—**Current Clinical Update: Emergency Medicine for the Primary Care Physician.** Saint Joseph Hospital, Denver. Fri. Contact: Kari Edwards, (303) 837-7297.

September 22-23—**ACLS Course.** Colorado Society of Anesthesiologists at St Luke's Hospital, Denver. Sat-Sun. Contact: Carol Goddard, (303) 770-6048.

October 10-11—**Physician Preceptorship Program.** The Children's Hospital, Denver. Wed-Thurs. Contact: Pat Winter, (303) 861-6668.

October 10-14—**Western Society of Allergy and Immunology—Annual Scientific Session.** Broadmoor Hotel, Colorado Springs. Wed-Sat. Contact: Becky Smith, (503) 279-8531.

October 13—**The Changing Faces of Medicine: Professional Decisions, Personal Choices.** Saint Joseph Hospital, Denver. Sat. Contact: Kari Edwards, (303) 837-7297.

October 17-19—**Care of the Sick Newborn Conference.** The Children's Hospital, Denver. Wed-Fri. Contact: Conference Dept, Children's Hospital, (303) 861-6945.

October 18—**Colorado Radiological Society.** Hyatt Regency DTC, Denver. Thurs. Contact: Carol Goddard, (303) 770-6048.

October 18—**Colorado Society of Clinical Pathologists.** Denver, location to be announced. Thurs. Contact: Carol Goddard, (303) 770-6048.

October 22-26—**Rural Perinatal Traineeship (Level 1).** The Children's Hospital, Denver. Mon-Fri. Contact: Christie Sievers, (303) 861-5413.

October 27—**Rocky Mountain Hand Surgery Society.** Denver, location to be announced. Thurs. Contact: Carol Goddard, (303) 770-6048.

November 2-3—**Fort Collins Perinatal Conference.** The Children's Hospital at the Marriott Hotel, Fort Collins. Fri-Sat. Contact: Christie Sievers, (303) 861-6413.

November 9-10—**Western Slope Conference.** The Children's Hospital at the Red Lion Inn, Durango. Fri-Sat. Contact: Christie Sievers, (303) 861-6413.

November 12-16—**Rural Perinatal Traineeship (Level II).** The Children's Hospital, Denver. Mon-Fri. Contact: Christie Sievers, (303) 861-6413.

November 15—**Colorado Radiological Society.** Hyatt Regency DTC, Denver. Thurs. Contact: Carol Goddard, (303) 770-6048.

December 3-7—**Respiratory Therapy Traineeship.** The Children's Hospital, Denver. Mon-Fri. Contact: Jeff Griebel, (303) 861-6227.

January—**Perinatal Continuing Education Program.** The Children's Hospital, Denver Community Hospital-based, 40-week, self-study program for all perinatal healthcare providers. Contact: Pat Winter, (303) 861-6668.

January 17—**Colorado Radiological Society.** Hyatt Regency DTC, Denver. Thurs. Contact: Carol Goddard, (303) 770-6048.

January 26-31—**Uvetitis and Pathology.** Colorado Ophthalmological Society at Westin Hotel, Vail. Sat-Thurs. Contact: Carol Goddard, (303) 770-6048.

First Wednesday of each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver, CO. (303) 270-5195.

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The Western Journal of Medicine
(ISSN 0093-0415/USPS 084 480) is published monthly for $35 per year (USA and Canada) by the California Medical Association, 221 Main Street, San Francisco, CA 94105. Second-class postage paid at San Francisco, CA and additional mailing offices.
POSTMASTER: Send address changes to *The Western Journal of Medicine*, Circulation, P.O. Box 7602, San Francisco, CA 94120-7602.

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Sponsored by the University of Washington School of Medicine, Department of Medicine, Department of Orthopaedics, and Office of Continuing Medical Education.

For information call the Office of Continuing Medical Education, (206) 543-1050. Registration fees are $220 by August 14, and $250 after August 14.

CONTINUING MEDICAL EDUCATION

(Continued from Page 206)

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

August 16—**Neonatal Resuscitation.** St Vincent Hospital, Santa Fe. Thurs. Contact: Jennifer Johnson, MD, 455 St Michael's Dr, Santa Fe 87501. (505) 983-3361.

September 6-8—**Perinatal Care Update.** Hilton Hotel, Albuquerque. Thurs-Sat. Contact: UNM SOM, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

September 7—**The Wounded Healer: Becoming a Healthy Healer.** Memorial Hospital, Albuquerque. Fri. Contact: Janice Frank, 806 Central, SE, Albuquerque 87102. (800) 448-9238 or (505) 247-0220.

September 14-15—**Essentials of Health Care for the Elderly.** Albuquerque Convention Center. Fri-Sat. Contact: UNM Office of Continuing Medical Education, PO Box 713, Albuquerque 87131. (505) 277-3942.

September 21-22—**Southwest Psychiatric Symposium on Substance Abuse.** Hyatt Regency, Albuquerque. Fri-Sat. Contact: UNM Office of Continuing Medical Education, PO Box 713, Albuquerque 87131. (505) 277-3942.

October 4-6—**Management of Radiation Accidents.** Sheraton Old Town Hotel, Albuquerque. Thurs-Sat. Contact: UNM Office of Continuing Medical Education, PO Box 713, Albuquerque 87131. (505) 277-3942.

October 11-13—**Second International Symposium on Intrapartum Biochemical Monitoring of the Fetus.** Hyatt Regency, Albuquerque. Thurs-Sat. Contact: UNM Office of Continuing Medical Education, PO Box 713, Albuquerque 87131. (505) 277-3942.

October 12-13—**John N. Wilson, MD: Lectureship in Cardiovacular Diseases.** Hyatt Regency, Albuquerque. Fri-Sat. Contact: Ann Nelson, Presbyterian Heart Institute Foundation, PO Box 26666, Albuquerque 87125. (505) 841-1225.

October 19-20—**Cancer Update 1990.** Clarion Four Seasons Hotel, Albuquerque. Fri-Sat. Contact: UNM Office of Continuing Medical Education, PO Box 713, Albuquerque 87131. (505) 277-3942.

October 20-21—**Common Problems in Pediatric Pulmonary Disease.** Santa Fe Hilton. Sat-Sun. Contact: Joe Dean, MD, 813 N Washington, Roswell 88201. (505) 622-2606.

October 25-27—**Primary Care Update '90.** University of New Mexico Conference Center, Albuquerque. Thurs-Sat. Contact: UNM School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

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CONTINUING MEDICAL EDUCATION

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UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

September 12-14—**Utah Medical Association—Annual Meeting.** Marriott, Salt Lake City. Wed-Fri. Contact: UMA.

October 4-5—**Ethics and Health** (Sponsor: UUMC). Thurs-Sat. University of Utah Alumni House, Salt Lake City. Contact: (801) 581-8664.

October 11-12—**Proper Prescribing of Controlled Substances** (Sponsor: UMA and UUMC). Thurs-Fri. University Park Hotel, Salt Lake City. Contact: UMA.

SPONSORS OF COURSES—ABBREVIATIONS

AHA:	American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.
BYUHS:	Brigham Young University Health Services, McDonald Student Health Center, Brigham Young University, Provo 84602. (801) 378-2771.
CH:	Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.
CWH:	Cottonwood Hospital, 5770 S 300 East, Salt Lake City 84101. (801) 262-3461.
DMC:	Dixie Medical Center, 544 S 400 East, St George 84770. (801) 673-9681.
HCH:	Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.
ITS:	Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH:	LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH:	Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.
MVH:	Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.
144:	144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.
OSS:	Ogden Surgical Society, PO Box 9311, Ogden 84409.
PCMC:	Primary Children's Medical Center, 320 12th Ave, Salt Lake City 84103. (801) 363-1221.
PVH:	Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
SMH:	St Mark's Hospital, 1200 E 3900 South, Salt Lake City 84117. (801) 268-7111.
UMA:	Utah Medical Association, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
UOS:	Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

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Practical Management of Drug, Alcohol, and Tobacco Abuse Problems within the Primary Care Population

Friday and Saturday
October 5-6, 1990
Seattle, Wash.

- Assessment and management techniques for managing substance-abusing patients
- Guidelines for doctors to use with drug and alcohol abusers
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For information call the Office of Continuing Medical Education, (206) 543-1050. Registration fees are $240 by September 5, $265 after September 5.

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CONTINUING MEDICAL EDUCATION

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USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUMC: University of Utah Medical Center, 50 N Medical Dr, Salt Lake City 84132. (801) 581-2258.

UVRMC: Utah Valley Regional Medical Center, 1034 N Fifth West, Provo 84604. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

VVMC: Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

August 13-18—**Summer Seminar in Health Care Ethics.** Seattle. Mon-Fri. Contact: U/W.

September 10—**Cerebral Palsy Seminar.** Spokane. Mon. Contact: (509) 327-9521.

September 10-14—**Family Practice Review.** Seattle. Mon-Fri. Contact: U/W.

September 14-15—**Management of Sarcoma.** Seattle. Fri-Sat. Contact: U/W.

September 20—**Orthopedics.** Everett. Thurs. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

September 20-21—**Critical Care '90.** Tacoma. Thurs-Fri. Contact: Multicare, (206) 594-1221.

September 26—**Rheumatology.** Seattle. Wed. Contact: Northwest Hospital, (206) 368-1622.

October 11—**Diabetes.** Everett. Thurs. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

October 12—**Attorneys and Medicine.** Seattle. Fri. Contact: U/W.

October 16-19—**Indoor Radon and Lung Cancer: Reality or Myth.** Richland. Tues-Fri. Life Sciences Center, Battelle, Pac NW Lab. (509) 376-3665.

October 19—**24th Annual Cancer Conference: Gastrointestinal Cancer in the '90s.** Seattle. Fri. Contact: VMMC.

October 20—**Practice Update for Rural Physicians.** Seattle. Sat. Contact: VMMC.

October 24—**Sexual Dysfunction.** Seattle. Wed. Contact: Northwest Hospital, (206) 368-1622.

November 2—**Diabetes, 1990.** Seattle. Fri. Contact: VMMC.

November 8—**Pediatrics.** Everett. Thurs. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

November 9—**Medical and Surgical Update for Psychiatrists.** Seattle. Fri. Contact: VMMC.

November 14—**Psychiatry.** Seattle. Wed. Contact: Northwest Hospital, (206) 368-1622.

November 15-16—**Drug Therapy.** Seattle. Thurs-Fri. Contact: U/W.

December 7—**Practical Pediatrics.** Seattle. Fri. Contact: VMMC.

December 8—**Gastrointestinal Conference.** Seattle. Sat. Contact: Northwest Hospital, (206) 368-1622.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898. ◆

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YOHIMBINE HCl

Description: Yohimbine is a 3a-15a-20B-17a-hydroxy Yohimbine-16a-carboxylic acid methyl ester. The alkaloid is found in Rubaceae and related trees. Also in Rauwolfia Serpentina (L) Benth. Yohimbine is an indolalkylamine alkaloid with chemical similarity to reserpine. It is a crystalline powder, odorless. Each compressed tablet contains (1/12 gr.) 5.4 mg of Yohimbine Hydrochloride.

Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalmic centers and release of posterior pituitary hormone.

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Indications: Yocon® is indicated as a sympathicolytic and mydriatric. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.[1,2] Also dizziness, headache, skin flushing reported when used orally.[1,3]

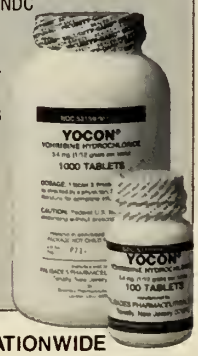
Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.[1,3,4] 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to ½ tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.[3]

How Supplied: Oral tablets of Yocon® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

Rev. 1/85



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The original manuscript and *two* copies should be submitted on heavy bond paper (8½ by 11 inches, *not* erasable), typed *double-spaced throughout* (including legends, tables, and references) on one side of the paper, with 1½-inch margins. Articles should not exceed 3,000 words (less than 15 text pages typed double-spaced). Under exceptional circumstances only will articles longer than 4,000 words be published. Pages should be numbered consecutively, beginning with the title page. Manuscripts produced with a dot-matrix printer are ordinarily not acceptable.

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Abbreviations. Use of abbreviations should be minimized. If they are necessary, abbreviations should be spelled out at first mention, with the abbreviation itself immediately following in parentheses.

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Titles are best when brief and concise. The title page should include the full name of the author(s), with degrees, academic or professional titles, complete addresses, and any institutional or other affiliations. The complete name and address of the person who will handle reprint requests also should appear on this page.

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The abstract (approximately 150 words) should be a short summary, saying in brief what is said at length in the body of the article—rather than such and such "is discussed," "is presented," or "was investigated."

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Each table should be typed on a separate sheet of paper, be numbered consecutively in Arabic numerals, have a brief descriptive title, and have its position indicated in the text.

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Three sets of clear, unmounted black and white glossy prints of figures should be submitted (preferably 5 by 7 inches, but no larger than 8½ by 11 inches). For line drawings, original artwork or glossy prints are acceptable. Illustrations should be numbered consecutively in Arabic numerals and the position indicated in the text. Figure number, first author's name and top of the photo should be shown on the reverse side of each illustration. Recognizable photographs of patients are to be masked and written permission for publication obtained from the patients.

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References should be limited to those cited in the text and should be to medical, scientific, or scholarly publications. (Mass circulation periodicals are referenced in parentheses in the text.) They must be typed double-space and numbered consecutively as they appear in the manuscript. (See examples below for style.) Abbreviations of journal titles should conform to those used in *Index Medicus*.

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Note handling of multiple authorship. If more than three authors are listed as contributors, use "et al" to designate those names after the first three. Also note capitalization, punctuation, use of inclusive page numbers, and year of publication. Separate the subtitle from the title by either a dash or a colon. Use colon *only* if it appears in the original citation.

1. Jones JS, Anderson HW, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978; 292:444-456
2. Graybill JR, Alford RH, Smith RG, et al: Cell-mediated immunity in cryptococcosis: A brief review. Cell Immunol 1978; 7:76-79

Books

Note handling of "edition," "editor(s)," and "volume," as well as appropriate sequence of reference information and capitalization of chapters and titles.

3. Berne EJ, Smith TL: Role playing in therapy, chap 2, Principles of Group Therapy. New York, Oxford University Press, 1966, pp 35-51 *(author of chapter same as author of book)*
4. Munsung JM: The role of drugs, chap 2, *In* Brest AN, Mayer JH (Eds): Hypertension—Vol 2, Therapy, 2nd Ed. Springfield, Ill, Charles C Thomas, 1961, pp 456-479 *(author of chapter different from authors of book)*

Pamphlets, Monographs, or Books With No Given Author

5. AMA Department of Drugs: AMA Drug Evaluation, 3rd Ed. Littleton, Mass, Publishing Sciences Group, 1977 *(corporate author)*
6. Compilation of Standard Definitions, 3rd Ed. Philadelphia, American Society for Testing and Materials, 1976 *(no given author; give name and place of publisher)*

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Any article accepted for publication should include the name of the journal (appropriately abbreviated) in which it will appear and the phrase "in press" or "accepted for publication" in place of the date of publication.

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Brief manuscripts commenting on articles that have appeared in the journal, containing information of interest to physicians, or discussing issues of the day will be considered for publication. Very short reports of cases, clinical experience, clinical studies, adverse effects, and the like also will be considered. Items for the Correspondence section should not exceed 600 words and should have no more than five bibliographic references and one figure or table.

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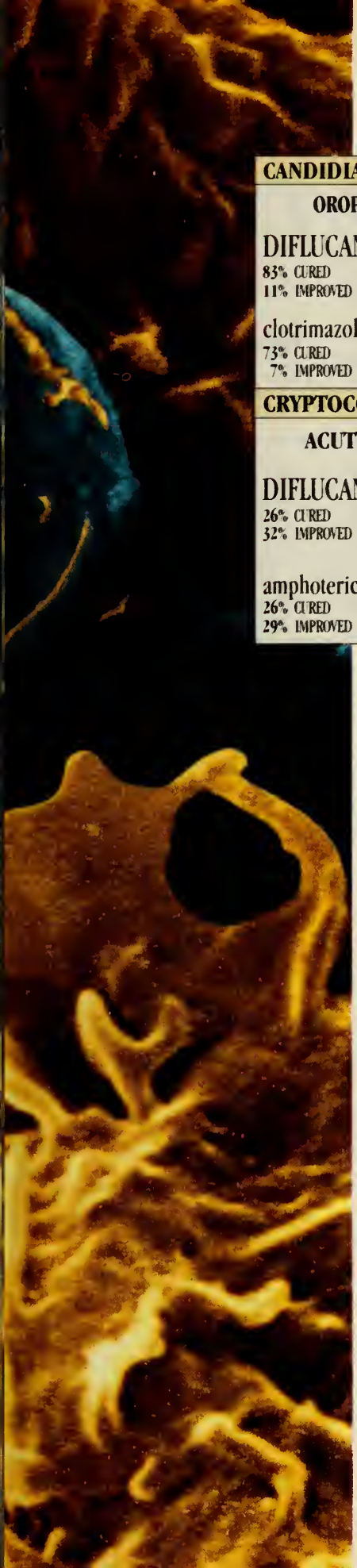
EFFECTIVELY TREATS MUCOSAL & SYSTEMIC FUNGAL INFECTIONS WITH FEW SAFETY CONCERNS

Neutrophil phagocytoses *Candida albicans*.

*Results of two randomized, third-party blinded, open-label trials using Diflucan 100 mg/day for 7 to 14 days; clotrimazole 50 mg/day for 14 days. Results reflect clinical cure and improvement.
†Endoscopic cure results of a double-blinded, randomized trial comparing Diflucan 100 to 200 mg/day; ketoconazole 200 to 400 mg/day.
‡Open-label trial. Diflucan 100 to 200 mg/day.
§Open-label, randomized trial. Clinical cure and improvement results. Diflucan 200 to 400 mg/day or amphotericin B 0.3 to 0.6 mg/kg/day.
‖Multicenter, comparative study. Results reflect successful maintenance without culture confirmed relapse as evaluated at a median of 212 days for Diflucan and 121 days for amphotericin B. Diflucan: 200 mg/day; amphotericin B: 1 mg/kg/week.



Excellent clinical success in oropharyngeal, esophageal, and systemic candidiasis, and cryptococcal meningitis:

Interim results from ongoing studies; due to the interim nature of these studies, statistics have not been provided.

CANDIDIASIS[1*]					
OROPHARYNGEAL[1*]		ESOPHAGEAL[1†] (endoscopic cures)		SYSTEMIC[1‡]	
DIFLUCAN 83% CURED 11% IMPROVED	94% (61/65)	DIFLUCAN	87% (20/23)	DIFLUCAN 63% CURED 23% IMPROVED	86% (189/219)
clotrimazole 73% CURED 7% IMPROVED	80% (36/45)	ketoconazole	53% (9/17)		

CRYPTOCOCCAL MENINGITIS			
ACUTE THERAPY[1§]		MAINTENANCE TO PREVENT RELAPSE[1‖]	
DIFLUCAN 26% CURED 32% IMPROVED	58% (54/93)	DIFLUCAN	98% (104/106)
amphotericin B 26% CURED 29% IMPROVED	55% (32/58)	amphotericin B	83% (64/77)

Excellent safety profile and patient compliance

In over 4,000 patients who received Diflucan for at least 7 days, the most common adverse events were nausea (3.7%), headaches (1.9%), and skin rash (1.8%).[1]

Rare incidence of serious hepatotoxicity has been reported, but the causal relationship to Diflucan is uncertain.[1]

Penetration to key tissues, organs, and fluids

Distribution throughout the body approximates that of total body water after oral or IV dosing.[1]

Oral bioavailability of Diflucan >90% and unaffected by agents that increase gastric pH.[1]

NOW ON MEDI-CAL

ONCE-A-DAY

Diflucan® ORAL / IV

(fluconazole)

100 mg, 200 mg Tablets / 200 mg, 400 mg IV Injection

The Antifungal Effectiveness You Need.
The Safety Profile You Want.

Please see brief summary of prescribing information on last page of this advertisement

ONCE-A-DAY Diflucan® ORAL / IV (fluconazole)

100 mg, 200 mg Tablets / 200 mg, 400 mg IV Injection

WITH ONCE DAILY DOSING FOR A WIDE RANGE OF PATIENTS

INDICATION	FIRST DAY	DAILY THERAPY	MINIMUM DURATION OF THERAPY
OROPHARYNGEAL CANDIDIASIS:	200 mg	100 mg	14 days
ESOPHAGEAL CANDIDIASIS:	200 mg	100 mg*	21 days
SYSTEMIC CANDIDIASIS:	400 mg	200 mg	28 days
CRYPTOCOCCAL MENINGITIS (acute):	400 mg	200 mg*	10-12 weeks after CSF becomes culture negative
CRYPTOCOCCAL MENINGITIS (maintenance to prevent relapse):	200 mg	200 mg	

*Doses of up to 400 mg/day may be used based on medical judgement of the patient's response to therapy.

References: 1. Data on file, Roerig division of Pfizer Pharmaceuticals

INDICATIONS AND USAGE

DIFLUCAN (fluconazole) is indicated for the treatment of:

1. Oropharyngeal and esophageal candidiasis. DIFLUCAN is also effective for the treatment of serious systemic candidal infections, including urinary tract infection, peritonitis, and pneumonia.

2. Cryptococcal meningitis.

Specimens for fungal culture and other relevant laboratory studies (serology, histopathology) should be obtained prior to therapy to isolate and identify causative organisms. Therapy may be instituted before the results of the cultures and other laboratory studies are known, however, once these results become available, antiinfective therapy should be adjusted accordingly.

CONTRAINDICATIONS

DIFLUCAN (fluconazole) is contraindicated in patients who have shown hypersensitivity to fluconazole or to any of its excipients. There is no information regarding cross hypersensitivity between fluconazole and other azole antifungal agents. Caution should be used in prescribing DIFLUCAN to patients with hypersensitivity to other azoles.

WARNINGS

Patients who develop abnormal liver function tests during DIFLUCAN therapy should be monitored for the development of more severe hepatic injury. Although serious hepatic reactions have been rare and the causal association with DIFLUCAN uncertain, if clinical signs and symptoms consistent with liver disease develop that may be attributable to fluconazole, DIFLUCAN should be discontinued. (See Adverse Reactions.)

Immunocompromised patients who develop rashes during treatment with DIFLUCAN should be monitored closely and the drug discontinued if lesions progress. (See Adverse Reactions.)

PRECAUTIONS

Drug Interactions (See Clinical Pharmacology)

DIFLUCAN (fluconazole) increased the prothrombin time after warfarin administration. Careful monitoring of prothrombin time in patients receiving DIFLUCAN and coumarin-type anticoagulants is recommended.

DIFLUCAN increased the plasma concentrations of phenytoin. Careful monitoring of phenytoin concentrations in patients receiving DIFLUCAN and phenytoin is recommended.

DIFLUCAN has been infrequently associated with an increase in cyclosporine concentrations in renal transplant patients with or without impaired renal function. Careful monitoring of cyclosporine concentrations in patients receiving DIFLUCAN and cyclosporine is recommended.

DIFLUCAN increased the plasma concentrations and reduced the metabolism of tolbutamide, glyburide and glipizide. When DIFLUCAN is used concomitantly with these or other sulfonylurea oral hypoglycemic agents, blood glucose concentrations should be carefully monitored, and the dose of the sulfonylurea should be adjusted as necessary.

Rifampin enhances the metabolism of concurrently administered DIFLUCAN. Depending on clinical circumstances, consideration should be given to increasing the dose of DIFLUCAN when it is administered with rifampin.

Physicians should be aware that drug-drug interaction studies with other medications have not been conducted, but such interactions may occur.

Carcinogenesis, Mutagenesis and Impairment of Fertility

Fluconazole showed no evidence of carcinogenic potential in mice and rats treated orally for 24 months at doses of 2.5, 5 or 10 mg/kg/day (approximately 2-7x the recommended human dose). Male rats treated with 5 and 10 mg/kg/day had an increased incidence of hepatocellular adenomas.

Fluconazole, with or without metabolic activation, was negative in tests for mutagenicity in 4 strains of *S. typhimurium*, and in the mouse lymphoma L5178Y system. Cytogenetic studies *in vivo* (murine bone marrow cells, following oral administration of fluconazole) and *in vitro* (human lymphocytes exposed to fluconazole at 1000 μg/mL) showed no evidence of chromosomal mutations.

Fluconazole did not affect the fertility of male or female rats treated orally with daily doses of 5, 10 or 20 mg/kg or with parenteral doses of 5, 25 or 75 mg/kg, although the onset of parturition was slightly delayed at 20 mg/kg p.o. In an intravenous perinatal study in rats at 5, 20 and 40 mg/kg, dystocia and prolongation of parturition were observed in a few dams at 20 mg/kg (approximately 5-15x the recommended human dose) and 40 mg/kg, but not at 5 mg/kg. The disturbances in parturition were reflected by a slight increase in the number of stillborn pups and decrease of neonatal survival at these dose levels. The effects on parturition in rats are consistent with the species specific estrogen-lowering property produced by high doses of fluconazole. Such a hormone change has not been observed in women treated with fluconazole. (See Clinical Pharmacology.)

Pregnancy

Teratogenic Effects. Pregnancy Category C: Fluconazole was administered orally to pregnant rabbits during organogenesis in two studies, at 5, 10 and 20 mg/kg and at 5, 25, and 75 mg/kg respectively maternal weight gain was impaired at all dose levels, and abortions occurred at 75 mg/kg (approximately 20-60x the recommended human dose), no adverse fetal effects were detected. In several studies in which pregnant rats were treated orally with fluconazole during organogenesis, maternal weight gain was impaired and placental weights were increased at 25 mg/kg. There were no fetal effects at 5 or 10 mg/kg, increases in fetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25 and 50 mg/kg and higher doses. At doses ranging from 80 mg/kg (approximately 20-60x the recommended human dose) to 320 mg/kg embryolethality in rats was increased and fetal abnormalities included wavy ribs, cleft palate and abnormal craniofacial ossification. These effects are consistent with the inhibition of estrogen synthesis in rats and may be a result of known effects of lowered estrogen on pregnancy, organogenesis and parturition.

There are no adequate and well controlled studies in pregnant women. DIFLUCAN should be used in pregnancy only if the potential benefit justifies the possible risk to the fetus.

Nursing Mothers

It is not known whether fluconazole is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when DIFLUCAN is administered to a nursing woman.

Pediatric Use

Efficacy of DIFLUCAN has not been established in children. A small number of patients from age 3 to 13 years have been treated safely with DIFLUCAN using doses of 3-6 mg/kg daily.

ADVERSE REACTIONS

Sixteen percent of over 4000 patients treated with DIFLUCAN (fluconazole) in clinical trials of 7 days or more experienced adverse events. Treatment was discontinued in 1.5% of patients due to adverse clinical events and in 1.3% of patients due to laboratory test abnormalities.

In combined clinical trials and foreign marketing experience prior to U.S. marketing, patients with serious underlying disease (predominantly AIDS or malignancy) rarely have developed serious hepatic reactions or exfoliative skin disorders during treatment with DIFLUCAN (See Warnings). Two of these hepatic reactions and one exfoliative skin disorder (Stevens-Johnson syndrome) were associated with a fatal outcome. Because most of these patients were receiving multiple concomitant medications, including many known to be hepatotoxic or associated with exfoliative skin disorders, the causal association of these reactions with DIFLUCAN therapy is uncertain.

Clinical adverse events were reported more frequently in HIV infected patients (21%) than in non-HIV infected patients (13%), however, the patterns in HIV infected and non-HIV infected patients were similar. The proportions of patients discontinuing therapy due to clinical adverse events were similar in the two groups (1.5%).

The following treatment-related clinical adverse events occurred at an incidence of 1% or greater in 4048 patients receiving DIFLUCAN for 7 or more days in clinical trials: nausea 3.7%, headache 1.9%, skin rash 1.8%, vomiting 1.7%, abdominal pain 1.7%, and diarrhea 1.5%.

In two comparative trials evaluating the efficacy of DIFLUCAN for the suppression of relapse of cryptococcal meningitis, a statistically significant increase was observed in median AST (SGOT) levels from a baseline value of 30 IU/L to 41 IU/L in one trial and 34 IU/L to 66 IU/L in the other. The overall rate of serum transaminase elevations of more than 8 times the upper limit of normal was approximately 1% in fluconazole-treated patients in clinical trials. These elevations occurred in patients with severe underlying disease, predominantly AIDS or malignancies, most of whom were receiving multiple concomitant medications, including many known to be hepatotoxic. The incidence of abnormally elevated serum transaminases was greater in patients taking DIFLUCAN concomitantly with one or more of the following medications: rifampin, phenytoin, isoniazid, valproic acid, or oral sulfonylurea hypoglycemic agents.

65-4526-00-0

Issued Jan. 1990

Pfizer Roerig

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SPECIAL ISSUES

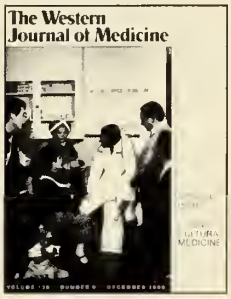
Addiction Medicine
and the Primary Care Physician

Addiction Medicine and the Primary Care Physician was conceived to be part of the initiative to expand the involvement of all specialties of medicine in the prevention and treatment of addictive disease. Topics covered include chemical dependence and the workplace, alcoholism, methadone maintenance in the treatment of opioid dependence, nicotine dependence, and treatment of cocaine dependence. David Smith MD, Special Editor, 1990.

Women and Medicine

This special issue explores both the professional side of women in medicine and the diagnosis and treatment of women patients. Topics covered include liver disease, women and AIDS, heart disease, hysterectomy, PMS, ovarian cancer, and women physicians and organized medicine. Linda Hawes Clever, MD, Special Issue Editor, 1988.

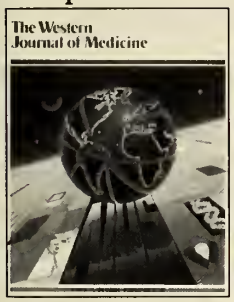
Cross-cultural Medicine



Cross-cultural medicine is devoted to the care of patients of different cultural, ethnic, or religious backgrounds. Subjects include Southeast Asian refugees in the American health care system, psychiatry and Chinese culture, health and illness in Filipino immigrants, and health care of Middle Eastern patients. M. Margaret Clark, PhD, Special Issue Editor, 1983. 2nd reprinted edition.

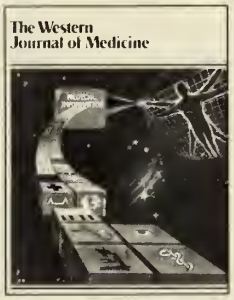
Also available:

AIDS—A Global Perspective



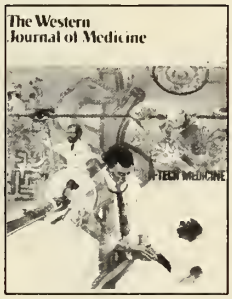
Jonathan M. Mann, MD
Special Issue Editor, 1987

Medical Informatics



Marsden S. Blois, MD
Special Issue Editor, 1986

High-Tech Medicine



R. Paul Robertson, MD
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Western States OPENINGS

Many multispecialty groups and hospitals have asked us to recruit for over 300 positions of various specialties. Both permanent and locum tenens. Send CV to:

Western States Physician Services
5414 E. Montecito, Fresno, CA 93727
Or call 1 (800) 873-0786

RADIOLOGIST. Part-time position available immediately in small hospital with general radiography and fluoroscopy, mammography, and ultrasound in Weaverville, California. Contact Drs Wheeler, Biggs, or Babbitt, West Coast Radiology, 3798 Janes Rd, Ste 12, Arcata, CA 95521; office number (707) 822-3621, ext 191.

PHYSICIAN OPPORTUNITIES IN ARIZONA. Thomas-Davis Medical Centers, PC, a rapidly expanding multispecialty group practice of 90 plus physicians in Tucson, Green Valley, and Tempe, Arizona, has positions available in these cities in Internal Medicine, Pediatrics, OB/GYN, Orthopedics, Urgent Care, and Family Practice. Excellent fringe benefits and profit sharing program. Fee-for-service, as well as owned HMO. Must be BE/BC. Call or write James J. Vitali, CEO, Thomas-Davis Medical Centers, PC, PO Box 12650, Tucson, AZ 85732; (602) 322-8300.

INTERNAL MEDICINE. Long established multispecialty group in central Washington needs Internist. Independent contract or join partnership later. University town with many cultural and recreational activities. Send CV to Medical Building Associates, 200 E. 6th, Ellensburg, WA 98926, or call (509) 925-9891.

MULTIPLE FAMILY PRACTICE (BC/BE) positions available in several suburban satellite clinics of a large Seattle area multispecialty group practice. Diverse patient population includes managed care, fee-for-service, and retired military (at some satellite clinics). Competitive salary and excellent benefits. Contact Mary Anderson, Pacific Medical Center, 1200 12th Ave S., Seattle, WA 98144; (206) 326-4111.

HAWAII. Family Practitioner needed for rural underserved area. Full-time position in nonprofit community health clinic. No OB, hospitalizations optional. Desire dedicated person to work in multicultural setting. Contact Alan Chun, MD, Waianae Coast Comprehensive Health Center, 86-260 Farrington Hwy, Waianae, HI 96792; (808) 696-7081.

PHYSICIANS WANTED

CALIFORNIA

Primary Care Physicians and Radiologists needed to work as *locum tenens* statewide. High salary, paid malpractice. Work whenever and wherever you wish. Permanent placements as well. **Western Physicians Registry: Northern California, contact Jim Ellis, Director, (415) 673-7676 or (800) 437-7676. Southern California, contact Tracy Zweig, Director, (805) 643-9346 or (800) 635-3175.**

CALIFORNIA MULTISPECIALTY. Cardiologist, Internal Medicine, Pediatrician, Endocrinologist, Orthopedist, General/Family Practitioner, Obstetrician/Gynecologist, Dermatologist, Ophthalmologist, General Surgeon, Podiatrist. Excellent opportunity for physicians in Los Angeles suburb to join 100 member multispecialty medical group. Large fee-for-service and prepaid practice, no Medi-Cal. Excellent compensation program based on guarantee plus incentive, profit sharing and pension plan. Group provides health, dental, life, and malpractice. Partnership in real estate and medical corporation available. Send CV to Ron McDaniel, Assistant Administrator, Mullikin Medical Center—5, 17821 S. Pioneer Blvd, Artesia, CA 90701.

OB/GYN. BC/BE to join 20 physician (OB, Pediatrics, Internal Medicine) practice in sunny central Washington. Reasonable call schedule with three OB/GYN department. Competitive salary, excellent benefit package including vacation at 30 days per year and professional liability. Contact Ann Garza, Yakima Valley Farm Workers Clinic, PO Box 190, Toppenish, WA 98948; (509) 865-5898.

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Let us find you the practice that meets your specifications and geographical preference. There is no fee to the physician for our professional service. All inquiries are held in strict confidence. BC/BE physicians send CV or call:

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Mac Kenzie & Associates
PO Box 1240
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PHYSICIANS WANTED

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SAN FERNANDO VALLEY, CA
Family Physician
Internist
OB/GYN
Orthopedic Surgeon (Backs)

DENVER, COLORADO
Family Physician
Internist

For other opportunities in these states, send your CV to: Gordon Crawford, Manager, Professional Relations, Humana Inc., Dept. HH-8, 500 West Main Street, Louisville, KY 40201-1438. Or call TOLL-FREE 1-800-626-1590.

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OB/GYN, INTERNISTS, Family Practitioners, Pediatricians for Arizona and western opportunities. Quality positions available other regions of country. Inquiries confidential. Mitchell & Associates, PO Box 1804, Scottsdale, AZ 85252; (602) 990-8080.

NEAR STANFORD. Six Internists, all subspecialty trained and members of clinical faculty at Stanford, interested in an associate with subspecialty interest and training. Should be well grounded in Internal Medicine. Send CV to Dr Bigler, El Camino Internal Medical Group, 125 South Dr, Mountain View, CA 94040.

CALIFORNIA—NORTHERN. Area's leading private practice group has immediate and future positions for BC/BE Family Practice and Primary Care Physicians in its Department of Ambulatory Care and General Medicine. Excellent compensation, incentive program, full benefits, early equity position, retirement plan. Experience life-style and professional fulfillment in beautiful northern California. Call Maureen Forrester: (408) 282-7833. Send CV to San Jose Medical Group, Inc, 45 S. 17th St, San Jose, CA 95112.

OCCUPATIONAL MEDICINE PHYSICIAN. BC is preferred, but will consider physician with a strong background in Occupational Medicine. Competitive salary and benefits. Located in an outstanding community, the Santa Clarita Valley. If you would like to continue to use your clinical skills, yet also be involved in administrative decisions, please submit your CV to Richard Kessler, Director, Occup. Health Services, c/o SCV Healthcare Management Group, Valencia, CA 91355.

(Continued on Page 218)

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AIR FORCE

(Continued from Page 216)

PHYSICIANS WANTED

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The **County of Orange,** Health Care Agency, has an excellent ***Opportunity for Leadership*** in a dynamic public health department. We are seeking a **Deputy Public Health Officer** to serve as assistant health officer and focus on epidemiology as the basis for program development, and hold responsible authority for the health policy and medical management of the Public Health Function.

The **County of Orange,** located on the Southern California Coast, is an outstanding place to live, work and enjoy great recreational areas.

If you are interested in competing for this challenging opportunity, and if you possess (or are able to obtain by date of appointment) a valid California Physician's and Surgeon's Certificate ***AND*** have five years of increasingly responsible, related experience, please contact Joyce Allen, **(714) 834-5033,** to obtain recruitment materials. ***APPLY IMMEDIATELY!*** **County of Orange, Personnel Department, 10 Civic Center Plaza, Santa Ana, CA 92701.** Affirmative Action Employer M/F.

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Please contact: George Perlstein, M.D.
Medical Director
Palo Alto Medical Clinic
300 Homer Avenue, Palo Alto, CA 94301
(415) 853-4762

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PHYSICIANS WANTED

POSITION AVAILABLE

For BC/BE physicians in California, Oregon, and Washington: Anesthesia, Critical Care, Emergency Medicine, Endocrinology, Family Practice, Infectious Disease, Internal Medicine, Neurology, Neurosurgery, OB/GYN, Oncology, Ophthalmology, Orthopedics, Otolaryngology, Pediatrics, Thoracic Surgery, Urgent Care. **BRADSHAW ASSOCIATES, 21 Altamount Dr, Orinda, CA 94563; (415) 376-0762, FAX (415) 376-0813.**

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Dallas, Texas 75201
214/761-9200

PHYSICIANS WANTED

WASHINGTON STATE

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An expanding 70 physician multispecialty fee-for-service group seeks BC/BE physicians in the following specialties:

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CARDIOLOGY	HEMATOLOGY/ONCOLOGY
DERMATOLOGY	OB/GYN
INTERNAL MEDICINE	RHEUMATOLOGY
PEDIATRICS	GENERAL SURGERY
FAMILY PRACTICE	ORTHOPEDICS

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CONTACT: **Colleen Mooney, Recruitment Coordinator**
Rockwood Clinic, PS
E. 400 Fifth Ave
Spokane, WA 99202
(509) 838-2531

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415-556-3690
Public Health Service
50 United Nations Plaza
San Francisco, CA 94102

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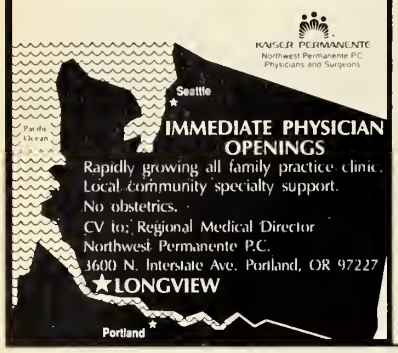
PHYSICIANS WANTED

LONGVIEW, WASHINGTON



Longview is a picturesque, stable community of 42,000 located near the Columbia Gorge and the coastal mountains and beaches of Washington and Oregon. Members of our 12 physician group enjoy individual subpractices, infrequent call, and new state-of-the-art medical offices.

We invite you to contact us at the above address regarding practice opportunities. Or call Judy Parmenter, Physician Recruitment, (503) 280-2050 for further information.

PHYSICIAN OPPORTUNITIES NATIONWIDE
For all specialties for hospitals, clinics, multispecialty groups, partnership and solos. Contact Jim Grant in complete confidence at the bay area specialists. **Nugent & Grant, Inc, 1400 Coleman, Ste B-22, Santa Clara, CA 95090; or call (800) 727-2478, FAX # (408) 727-7390.** Never a fee to the physician.

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URGENT CARE/PRIMARY CARE PHYSICIANS for over 90 positions available with various physician groups in Phoenix metropolitan/Tucson, Arizona. Excellent compensation and partnership opportunities. Contact Mitch Young, PO Box 1804, Scottsdale, AZ 85252; (602) 990-8080.

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CALIFORNIA, SANTA CLARA COUNTY. Positions currently available for experienced physicians to provide primary care services at hospital based Urgent Care Center in San Jose. Minimum guarantee of $100,000 plus annually for 42-hour work week, 48 weeks per year with paid malpractice. No night call. Please contact Nanette Peter, Associated Emergency Physicians, Inc, Medical Group of Northern California, 1625 The Alameda, Ste 201, San Jose, CA 95126; (408) 293-8881.

ALBUQUERQUE, NEW MEXICO. BC/BE Family Practitioners sought to join established, private practice, single specialty group practice. Income guarantee, benefits. Please send CV to Kathryn Rhoades, Presbyterian Healthcare Services, PO Box 26666, Albuquerque, NM 87125-6666, or call 1 (800) 545-4030, ext 6330.

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We are currently seeking highly qualified Internists and subspecialists to complement our energetic Internal Medicine team. Department members provide a full range of medical services for a population of over 200,000 pre-paid health plan members. Recently renovated and expanded medical center facilities are within convenient commuting distance to virtually any bay area city, and the extensive cultural and recreational activities of northern California. As part of our large, multispecialty group practice, you would enjoy an excellent salary, generous fringe benefits, a flexible schedule, and the opportunity for academic affiliation with prestigious local institutions. Send CV to:

Winslow Wong, MD
Attn: Administration
Kaiser Permanente Medical Center
27400 Hesperian Blvd
Hayward, CA 94545
EOE

NORTHERN CALIFORNIA—SAN FRANCISCO BAY AREA. Leading HMO is seeking BC/BE physician to staff a busy, urban, full-service Emergency Department with the possibility of administrative advancement. Kaiser Permanente is a large pre-paid HMO offering competitive salary, job security, shareholder status, and generous benefits including health care, life insurance, disability insurance, sick leave, mortgage assistance, and educational leave. Please address all inquiries to David Witt, MD, Emergency Department, Kaiser Permanente Medical Center, 1200 El Camino Real, ADWJM, South San Francisco, CA 94080-3299; or call (415) 742-2516. EOE.

MARYSVILLE (YUBA CITY). Primary care provider. Northern California primary care clinic with large Medi-Cal clientele. Three physicians, two physician assistants. No OB. No surgery. Near mountains, close to Sacramento, 2½ hours to Lake Tahoe and San Francisco. Salary $86,113 plus. Please contact Ed Allen, 938 14th St, Marysville, CA 95901; or call (916) 741-6244.

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PHYSICIANS WANTED

PHYSICIANS NEEDED

The continuing growth of our service area population (now 90,000) has created an immediate need for additional BC/8E physicians in the following specialities:

- **NEUROLOGY.** Establish private practice with no investment, guaranteed income. Proficiency in EEG, EMG required.
- **GENERAL/THORACIC SURGERY.** Establish private practice in General and Thoracic Surgery (no open heart) with no investment, guaranteed income.
- **ONCOLOGY.** Establish private practice with no investment, guaranteed income. Some General Internal Medicine necessary initially.
- **ORTHOPEDIC SURGERY.** No investment, guaranteed income. Above average earning potential.
- **EMERGENCY MEDICINE.** Hospital position. 8C/8E in Emergency Medicine, or equivalent combination of appropriate residency training and Emergency Medicine experience. California license required. Competitive remuneration, paid malpractice insurance, individual contract, flexible scheduling. CE allowance. Part-time for double coverage also available.
- **RADIOLOGY.** Hospital group position. Excellent salary and benefit package. Competency in ultrasound, CAT, Nuclear Medicine, film screen mammography, and general diagnosis required. MRI experience desired. Inpatient and outpatient. (California license is required.)

112-bed full service hospital, very well equipped. Excellent ancillary services. Our service area population is now 90,000; a growing area with new businesses and a stable economy.

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Contact:
Tulare District Hospital
Physician Recruiting Office
PO Box 90112
Los Angeles, CA 90009
(800) 468-2687

RADIOLOGIST FOR SOUTHEASTERN UTAH. Excellent practice opportunity to join second Radiologist. Primary service area of 30,000 people with 88-bed community hospital. Nuclear, CT, mammography, ultrasound, and radiography. Contact Milton Bauermeister, MD, Castleview Hospital, Price, UT 84501; (801) 637-4800, ext 280 or (801) 472-5403.

MD, 8C/8E in Occupational Medicine, Internal Medicine, Family Practice, or ER to join established free-standing Occupational Medicine clinic. Attractive opportunity for growth. Competitive salary and benefits. Send CV to Manager, M8I Industrial Medicine, Inc, 2539 N. 35th Ave, Phoenix, AZ 85009.

ORTHOPEDIC SURGEON. 8C Orthopedic Surgeon needed for office practice in beautiful southern California area. Full- or part-time, surgery optional. Excellent compensation package. Send CV to Ronald Gilbert, MD, c/o Gilbert Medical Group, 1076 E. First St, #A, Tustin, CA 92680; or call (714) 832-1516.

SACRAMENTO, CALIFORNIA. Two Occupational Medicine Physicians needed for urgent care clinics. Unique opportunity with no on-call or weekend hours. BE/BC in Occupational Medicine preferred but will consider Emergency Room, Internal Medicine, or Family Practice background. Compensation, benefits, and hours are negotiable. Positions are associated with an established multispecialist group. Excellent locale, affordable housing, quality support personnel, and equity position in the group is possible. Send CV to John Murphy, PHC Administration, 8110 Timberlake Way, Ste D, Sacramento, CA 95823.

(Continued on Page 221)

YOUR SPECIALTY IS WORTH AN EXTRA $8,000 A YEAR.

If you're a resident in any of the following specialties:

- anesthesiology
- orthopedic surgery
- general surgery
- neurosurgery
- colon/rectal surgery
- cardiac/thoracic surgery
- pediatric surgery
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- plastic surgery

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REGIONAL DIRECTOR, LTC THOMAS C. DAMRON
(415) 922-8985/8986

BE ALL YOU CAN BE.®
ARMY RESERVE

(Continued from Page 220)

PHYSICIANS WANTED

HEMATOLOGIST/ONCOLOGIST, CARDIOLOGIST FOR PUGET SOUND POSITION. Multispecialty group practice. Please send CV with reply to Number 212, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

ONCOLOGIST/HEMATOLOGIST, BC/BE to join busy established private practice in Los Angeles. First year guarantee with incentives. Position available fall, 1990. Please send CV to Number 213, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

ORTHOPEDIC SURGEONS, BC/BE sought for expanding group in Sacramento. Currently seeking experienced hand/upper extremity, spine, and general Orthopedists. Excellent growth and compensation potential. Limited call schedule, flexible hours, med/legal evaluations. Send CV to Number 214, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

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PHYSICIANS WANTED

ENDOCRINOLOGIST/INTERNIST. Seeking BC/BE to join busy consultative and primary care practice of Endocrinology and Diabetology in desirable San Francisco bay area location. Group model HMO setting offers opportunities for teaching and clinical research. Competitive starting salary commensurate with experience. Outstanding benefit package including vacation, educational leave; life, health, disability, and malpractice insurance; and excellent retirement plan. For more information, please respond with CV to J. Mason, MD, Permanente Medical Group, 260 International Cir, Department WJM, San Jose, CA 95119; or call (408) 972-6428. EOE.

GENERAL INTERNAL MEDICINE—NEVADA, CALIFORNIA, TEXAS, LOUISIANA, FLORIDA! Private practice opportunities available. For details, call Eloise Gusman, 1 (800) 535-7698 or send CV to PO Box 1685, Covington, LA 70434-1685.

FAMILY PRACTITIONER
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PEDIATRICIAN

Multispecialty group located in San Luis Obispo, California, seeks BC/BE physicians. Fringe benefits plus practice costs paid and shareholder status. Submit your CV to:

Physician Recruitment
San Luis Medical Clinic
1235 Osos St
San Luis Obispo, CA 93401

PHYSICIANS WANTED

CENTRAL CALIFORNIA FAMILY PRACTICE/GENERAL PRACTICE. We have an opening for a Family Practice Physician. Clinic is a 17,000 square foot primary care facility located near Bakersfield offering medical, dental, lab, x-ray, and pharmacy services. Excellent salary plus incentive, plus inpatient revenue and excellent benefit package. Call George Johnston (805) 845-3731 for details or write PO Box 457, Lamont, CA 93241.

LOOKING FOR A PRIMARY CARE INTERNAL MEDICINE/GERIATRIC position with challenging and appreciative patients, quality associates, tolerable schedules in an attractive community? Send CV to Julie A. Prazich, MD, Medical Director, Sharp Senior HealthCare, 3545 Fourth Ave, San Diego, CA 92103.

SALT LAKE CITY. Family Practice and Urgent Care. Excellent opportunity in southeast suburb. Patients from upper middle class. Practice is busy and growing rapidly. Excellent salary with partnership in one year. Send CV to Mark Anderson, MD, 580 E. 9400 South, Salt Lake City, Utah 84070; (801) 975-1600.

PSYCHIATRIST FOR ROCKY MOUNTAIN CITY. An impressive Rocky Mountain community in Montana seeks Psychiatrist for well managed mental health clinic. Opportunity to succeed the present medical director exists within the next two to three years. Position includes both inpatient and outpatient practice and program development. Community population is over 80,000 with two modern hospitals. Liberal financial package offered. For more information call Jacquelin Walker, 1 (800) 776-7330, or write E. G. Todd Associates, 8600 Farley, Ste 100, Overland Park, KS 66212.

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(Continued from Page 221)

PHYSICIANS WANTED

ASSOCIATED EMERGENCY PHYSICIANS, INC.
Medical Group of Northern California
1625 The Alameda, Suite 201
San Jose, CA 95126

Experienced Emergency Physicians with ACLS/ATLS certification needed to staff moderate volume Emergency Department located in San Francisco.

- Excellent opportunity for highly-skilled, personable physicians interested in teaching house staff and providing quality Emergency Care.
- Established Emergency Physician group with 13 years experience.
- Excellent compensation. Malpractice paid.

Please contact: Nanette Peter, Recruitment Coordinator
(408) 293-8881

AMBULATORY CARE, HAYWARD AND MODESTO. Thriving practices, attractive facilities. Competitive salary, profit-sharing, partnership, growth potential, paid malpractice. Contact Jane Dressler, California Emergency Physicians, 2101 Webster St, #1050, Oakland, CA 94612; (415) 835-7431. Outside of California, (800) 842-2619.

WASHINGTON STATE. 31 physician, multispecialty group is recruiting a BC/BE Family Physician for a 40-hour per week position in our clinic-based Immediate Care Center. Attractive salary and benefit package. No evening call or hospital commitment. Attractive farming and college community of 35,000 in southeastern Washington State. Inquiries and CV to Robert G. Caudill, MD, Walla Walla Clinic, 55 W. Tietan, Walla Walla, WA 99362; (509) 525-3720, ext 285.

OCCUPATIONAL MEDICINE, SAN FRANCISCO BAY AREA. Area's leading multispecialty private group practice is seeking BC/BE physician to join their expanding Department of Occupational Medicine. Range of practice includes pre-employment physicals, diagnostic evaluations, treatment of on-the-job injuries; comprehensive knowledge of all areas of Occupational Medicine. Competitive salary, plus incentive, excellent benefits, paid malpractice. Located in the South Bay which offers wonderful cultural/recreational activities, fine dining, outstanding climate and scenery, easy access to beach and mountains. For further information, please send CV or contact Maureen Forrester, San Jose Medical Group, Inc, 45 S. 17th St, San Jose, CA 95112.

OCCUPATIONAL PHYSICIAN. Major multispecialty group with large Occupational Medicine department is seeking a clinically oriented, BC/BE Occupational Medicine Physician or physician with other Board Certification and experience in Occupational Medicine. Please contact Dr Kim Fuller, Director, Occupational Medicine Dept, Sharp Rees-Stealy Medical Group, Inc, 2001 Fourth Ave, San Diego, CA 92101, or call (619) 699-1524.

ALASKA. A 10 physician multispecialty group in Anchorage is now seeking to add their second Neurologist. For more information send CV to Gordon Crawford, Manager, Professional Relations, Humana Inc, Dept. HH-8A, 500 W. Main St, Louisville, KY 40201-1438; or call toll-free 1 (800) 626-1590.

ALASKA. The only Vitro-Retinal specialist in Anchorage is now seeking an associate with similar skills. For more information send CV to Gordon Crawford, Manager, Professional Relations, Humana Inc, Dept. HH-8B, 500 W. Main St, Louisville, KY 40201-1438; or call toll-free 1 (800) 626-1590.

PHYSICIAN OPPORTUNITIES, NEVADA LAS VEGAS MEDICAL CENTERS

are seeking qualified Family Practice and Emergency Physicians for our busy multi-center, walk-in clinics. Flexible hours, generous benefits, starting salary over $125K plus bonus and incentive programs. Excellent locations in exciting Las Vegas/Laughlin area, offer numerous recreational activities and the finest entertainment. Send CV to:

Physician Recruiter
2061 East Sahara
Las Vegas, NV 89104

SUNNY TUCSON, INTERNAL MEDICINE. Long established, large, multispecialty group seeks Internist BC/BE. Excellent benefits, opportunity to join partnership after one to two years. Send CV to Linda Hicklin, GHMA Medical Centers, PO Box 40550, Tucson, AZ 85717.

UNIVERSITY OF CALIFORNIA, DAVIS MEDICAL CENTER. The University of California, Davis, Department of Emergency Medicine is searching for physicians residency trained or BC in Emergency Medicine. The Health Science Campus is located in Sacramento and serves a large area of northern California. The Emergency Department cares for over 60,000 patients a year. The Center operates as a Level One Trauma Center, has paramedic base station training responsibilities, and has a helicopter service. An approved Emergency Medicine Residency Program began in July 1990. Emergency Physicians supervise medical students, interns, and residents, in addition to having direct patient responsibilities. Support for clinical research is available to those interested. University compensation is competitive, and fringe benefits include health and dental insurance, three weeks paid vacation, one week continuing medical education, social security, UC retirement plan, 12 paid holidays per year, and full malpractice coverage. Send CV to Robert W. Derlet, MD, Chief, Division of Emergency Medicine, University of California, Davis, Medical Center, 2315 Stockton Blvd, Sacramento, CA 95817.

RADIOLOGIST—SAN FRANCISCO BAY AREA. Growing outpatient imaging practice with CT/MRI. Salary leading to partnership. Send CV to Murray Solomon, MD, 450 Sutter St, Ste 835, San Francisco, CA 94108; (415) 296-8654.

PHYSICIANS WANTED

EXCELLENT

FAMILY PRACTICE

OPPORTUNITY

ROCKWOOD CLINIC, P.S.—a network of Family Practice clinics (main building and six satellites) seeks BE/BC Family Practitioners to join these busy independent practices offering the full range of inpatient/outpatient services, including obstetrics. ADVANTAGES INCLUDE:

- Join the largest department within this multispecialty group (15 Family Practitioners)
- Immediate in-house specialty consultation
- Well trained administrative support to assist in business matters, while allowing autonomy regarding the decisions of your practice
- Attractive benefit package includes excellent salary leading to early shareholder status

SPOKANE, WASHINGTON (metropolitan population 350,000) offers very affordable housing, unlimited year-round recreation, excellent schools, and numerous cultural organizations.

CONTACT:
Colleen Mooney
Recruitment Coordinator
Rockwood Clinic
E. 400 Fifth Ave
Spokane, WA 99202
(509) 838-2531

WYOMING—EMERGENCY MEDICINE. Position available for experienced Emergency Physician (prefer BC/BE in Emergency Medicine) in Rock Springs, Wyoming. Annual ED census 15,000 plus. Excellent occurrence malpractice insurance. Excellent medical and nursing staff. Contact High Desert Emergency Physicians, PC, PO Box 2452, Rock Springs, WY 82902; or T. Michael Mains, MD, at (307) 362-3711.

INTERNIST—PACIFIC NORTHWEST. Excellent opportunity for BC/BE Internist to join group of five Internists in suburban Idaho community. Near urban referral center with good subspecialty backup. Also near superb hunting, fishing, camping, and skiing. Please call or refer résumé to Susan Davis, Administrator, Caldwell Internal Medicine Professional Association, 222 E. Elm, Caldwell, ID 83605; 1 (208) 459-4667.

CALIFORNIA, MONTEREY BAY. Full-/part-time positions available with Monterey Bay's largest and most successful Urgent Care network. Generous guarantee, incentive plan, and benefit package. Malpractice covered. Practice in California's most beautiful coastal recreational area. BC/BE Emergency Room Medicine or Family Practice specialists preferred. Contact Bob Morris, MD, FACEP, Doctors on Duty Medical Clinics, 223 Mt Hermon Rd, Scotts Valley, CA 95066; (408) 438-9341.

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PHYSICIANS WANTED

DOWNEY, LOS ANGELES COUNTY, Family Practitioner or General Internist. Immediate full-time opening for a primary care physician to a new Neurology/Stroke rehabilitation inpatient unit with ambulatory care population. Regular hours without nighttime or weekend call. Rancho Los Amigos Medical is a Los Angeles County hospital and a teaching hospital affiliated with the University of Southern California. Good opportunity for teaching and/or research. California license required. Rancho Los Amigos is an affirmative action equal opportunity employer. Interested individuals should send CV to Milton Fort, MD, Rancho Los Amigos Medical Center, Neuro/Stroke Service, Rm 7, 700 Annex, 7601 E. Imperial Hwy, Downey, CA 90242.

FAMILY PRACTITIONER to join three BC Family Practitioners in busy single specialty group offering excellent income and benefits package. Enjoy partnership in this successful group after one year without buy-in. Community just outside St. Cloud, Minnesota, offers extraordinary quality of life with beautiful parks, rivers and lakes, progressive schools, and a clean, friendly environment. Universities, shopping, dining, and other big city amenities available just one-half hour away. Send CV or call Bryan Bassett, Jackson and Coker, 115 Perimeter Center Pl, Ste WJMO, Atlanta, GA 30346; 1 (800) 544-1987.

LOS ANGELES. Small multispecialty group seeks second Pediatrician and OB/GYN to work with present physicians. Excellent compensation and benefits. Looking for long term partners. Call or send CV to Craig Kaner, All Care Medical Group, 2675 E. Slauson Ave, Huntington Park, CA 90255; (213) 589-6681.

PHYSICIANS WANTED

OB/GYN
(Flexible Hours)
BAY AREA

Opening for general OB/GYN BC/BE to provide coverage and regular OB for high risk group based at prestigious hospital. Gynecology experience can be arranged if desired. Excellent support services. 40 hours per week with flexible/concentrated scheduling. Could be suitable for commuters from other parts of California. Call:

Anders Karlman, Karlman Associates
1 (800) 634-3561

A GROWING RURAL COMMUNITY of 40,000 has openings for two General Surgeons to join a busy practice. Located in eastern New Mexico, Clovis boasts a 100-bed hospital. Salary first year; potential partnership in practice with a Urologist, a Vascular Surgeon, and two General Surgeons. If interested, please send your CV to Bill Norris, Southwest Community Health Services, Physician Recruitment, PO Box 26666, Albuquerque, NM 87125.

LAKE ARROWHEAD, CALIFORNIA. Immediate openings for Emergency Physicians to staff low volume emergency department in wonderful location. Directorship also available. Guaranteed $115,000 per year. Directorship $130,000 per year; paid malpractice. Contact Richard Gillespie, MD, Quantum Emergency Medical Associates, PO Box 2467, Santa Rosa, CA 95405; (707) 546-4199.

PHYSICIANS WANTED

PEDIATRICIAN BC/BE for hospital-based teaching practice. Interest and training in Neonatology and Critical Care Pediatrics preferred. Join three full-time Pediatricians, two full-time Neonatologists, and one full-time Pediatric Surgeon in hospital with Community Level NICN and busy inpatient and outpatient services. Paid malpractice. Salary negotiable based on training and experience. Submit CV and references to Patricia A. Dixon, MD, Director, Pediatrics/Neonatal Services, San Joaquin General Hospital, PO Box 1020, Stockton, CA 95201; (209) 468-6600. AA/EOE.

MEDICAL DIRECTOR. For 173-bed regional medical center in New Mexico city of 50,000 plus. Recent consolidation of two established hospitals has created need for medical director with 10 years minimum in practice. Relevant directorship experience desirable. Responsibilities will include physician recruitment, medical staff leadership and direction, planning, and monitoring of clinical and professional performance of physicians. Opportunity for limited private practice. Salary and benefits commensurate with qualifications. Please respond to James D'Agostino, Executive Director, Eastern New Mexico Medical Center, 405 W. Country Club Rd, Roswell, NM 88201; (505) 622-8170.

DENVER PSYCHIATRIST. Innovative team working with older adults. Med. evaluations, consultations, some supervision. $100K, plus benefits for full-time. Part-time also available. National Institute for Behavior Change, (303) 296-2244. Ask for Lois Munson.

ENDOCRINOLOGIST, SANTA FE, NEW MEXICO needed to join flourishing private practice. Contact Robert M. Bernstein, MD, at 1533-B St Francis Dr, Santa Fe, NM 87501.

THE PERMANENTE MEDICAL GROUP
NORTHERN CALIFORNIA

QUALITY

STABILITY

LEADERSHIP

GROWTH

SUPPORT

REWARDS

The Permanente Medical Group, the largest multispecialty group practice in the U.S., is undergoing explosive growth in its Northern California region: the San Francisco Bay Area, Sacramento and the Central Valley. Our rapid increase in membership has created practice opportunities throughout the region.

Our physician-managed group is part of the comprehensive Kaiser Permanente Medical Care Program. As a TPMG physician, you have access to the latest medical technology and resources, the support of colleagues in all subspecialties — and the opportunity to provide excellent health care without the burdens of managing a practice.

TPMG offers many benefits: scheduled time off with cross-coverage provided by your colleagues, continuing education, malpractice insurance, a substantial retirement program and special arrangements for physicians transferring from established practice. For complete information, call or send CV to: The Permanente Medical Group, Inc., Richmond Prescott, M.D., Physician Recruitment Services, Dept. WJM-7153, 1814 Franklin, 4th Floor, Oakland, CA 94612. (800) 777-4912. EOE

KAISER PERMANENTE
Good People. Good Medicine.

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PHYSICIANS WANTED

As one of the nation's oldest and largest managed health care companies, CIGNA Healthplan understands the environment and resources physicians need to practice quality medicine. Currently we have the following opportunities available:

PHYSICIAN ADMINISTRATOR

You will maintain an active clinical practice with a proportion of time dedicated to leadership and management of physician and support staff. Qualifications must include Board Certification in a clinical specialty and prior management experience.

OBSTETRICIAN/ GYNECOLOGISTS

Part-time, flexible schedules as well as full-time positions are available in Los Angeles and Orange counties.

PRIMARY AND SPECIALTY CARE

A variety of opportunities are available at our 30 health care centers throughout southern California.

We offer a highly competitive compensation and benefits package, malpractice insurance, and continuing medical education. To hear more about CIGNA Healthplan:

Call collect **(818) 500-6236** or send CV to:
Professional Recruitment Dept.
CIGNA Healthplans of CA
505 N. Brand Blvd, Ste 400-49
Glendale, CA 91203

PSYCHIATRISTS needed for six new California facilities. $100K—paid malpractice. Older MDs are invited to apply. Please send CV to Number 215, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

GENERAL SURGEON ON TRAUMA SERVICE. The University of California, San Francisco is seeking an academically oriented General Surgeon, at the Assistant Professor level, to be based at San Francisco General Hospital. Candidate must have particular interest in trauma and critical care, and should be eligible or certified in surgical critical care, with at least one year of experience in caring for critically ill surgical patients. Candidate must also have had extensive clinical training in clinical trauma care during residency, or have taken a trauma fellowship. Additionally, basic research experience in molecular biology is desired, and research experience or demonstrated productivity in some area is essential. Responsibilities will include work in the Intensive Care Unit, Trauma Service, and General Surgery Clinics. Interested individuals should submit CV to Frank Lewis, MD, Chief of Surgery, San Francisco General Hospital, Box 0807, San Francisco, CA 94143-0807. The University of California, San Francisco, is an Affirmative Action/Equal Opportunity Employer. Women and minorities are encouraged to apply.

NORTHERN CALIFORNIA. Immediate openings for Emergency, Family Practice, and General Internal Medicine physicians who desire to work in the wine country north of San Francisco. Positions available in moderate volume emergency departments and ambulatory care center. A unique opportunity is also available for Family Practice and Internal Medicine physicians who desire to practice Inpatient Medicine without the hassles of an office practice. Guaranteed $90-$110,000 per year; paid malpractice. Contact Richard Gillespie, MD, Quantum Emergency Medical Associates, PO Box 2467, Santa Rosa, CA 95405; (707) 546-4199.

PHYSICIANS WANTED

SOUTHWEST MEDICAL ASSOCIATES℠

LAS VEGAS

Our 60 physician multispecialty group seeks additional Family Practice, Internal Medicine, Urgent Care, Ambulatory Care, and Gastroenterology physicians. Practice in America's Vacationland-mountain sports, water sports, world class entertainment, ideal climate. Enjoy affordable housing, no state income tax, excellent schools/colleges. High starting salaries, plus incentive bonuses, no investment required. Benefits include malpractice insurance, paid vacation, relocation expenses, health and life insurance, retirement program, early shareholder status, continuing medical education, dues, subscriptions, etc. Call less than one day in seven. Top tertiary hospital. Teaching, research, and administration opportunities also available.

If interested, call me at (702) 877-8638 or send your CV to:
Jerry Reeves, MD, President, Southwest Medical Associates
PO Box 15645, Las Vegas, NV 89114

EUGENE CLINIC, EUGENE, OREGON

Dynamic 55 physician multispecialty group with seven locations seeks BC/BE physicians in the following specialties: Family Practice, Geriatrics, Occupational Medicine, Orthopedics, Psychiatry, Urgency Care, Urology. Eugene, attractive university town within 60 mile radius of Cascade Mountains and Oregon coast, offers superlative life-style, fine school system, active and varied cultural opportunities, and unlimited recreation. Qualified candidates send CV and three letters of reference to:

Physician Recruiter
1162 Willamette St
Eugene, OR 97401

BC/BE CARDIOLOGIST full-time hospital based practice. Invasive privileges available. Central San Mateo County. Send CV to Associated Medical Specialists, c/o Dr Allen Lapin, 222 W. 39th Ave, San Mateo, CA 94403.

OPPORTUNITY for full- and part-time Emergency Physicians. Excellent fee-per-patient load ratio. Malpractice paid. Also, Emergency Department/Family Practice positions for urgent care/industrial center. Send CV to Front Line Community Physicians, PO Box 10610, Santa Ana, CA 92711, or contact Medical Director at (714) 771-3290.

CALIFORNIA. Excellent opportunity for BC/BE Gastroenterologist to join large, established multispecialty group in Santa Monica. Attractive salary with benefits package, paid malpractice insurance, and eventual partnership. Plese send CV to Mr Joel Prell, CEO, 1260 15th St, Ste #1501, Santa Monica, CA 90404.

CENTRAL CALIFORNIA. Hospital based teaching opportunity for OB/GYN in a new Residency Program at the KMC. Ideal candidate is a team player with a strong desire to teach residents. This UCLA affiliate has a busy OB department with 5,000 deliveries per year. Please contact Mary Letterii, Vice President, Physicians Search Group, 120 Montgomery St, Ste 710, San Francisco, CA 94104; (415) 399-8840.

SOUTHERN CALIFORNIA. Young Family Practitioner with dynamic practice seeking associate for future partnership. Generous salary/guarantee and incentives package. New medical office near outstanding 300-bed community hospital. Growing community within one hour of beaches and mountains. Ken Baker, PSG, 120 Montgomery St, Ste 710, San Francisco, CA 94104; (415) 399-8840.

23 PHYSICIAN GROUP PRACTICE. Recent population growth and demand have created the need for several specialists including OB/GYN, Neurology, ENT, Cardiology, and Pediatrics in this 23 physician group practice. Situated 60 miles east of San Francisco, the group serves a local population of 35,000. Nearby skiing and boating, reasonable housing, and an excellent school system. Please contact Mary Letterii, Vice President, Physicians Search Group, 120 Montgomery St, Ste 710, San Francisco, CA 94104; (415) 399-8840.

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Good People Good Medicine

NORTHERN CALIFORNIA

Several positions available for Family Practice, Internal Medicine, and most medical subspecialties. We are a young, aggressive group in a well known prepaid group practice HMO organization with excellent benefits and a very reasonable call schedule. You will have a rewarding practice opportunity with ample time to enjoy the mountains and San Francisco which are nearby. If interested please call or send CV to Physician Recruitment, Administration, The Permanente Medical Group, Inc, 1305 Tommydon St, Stockton, CA 95210; (209) 476-3300.

CALIFORNIA—SAN JOSE. Director wanted for hospital-based Walk-In Clinic with 30,000 annual visits. Applicants should have prior administrative experience and be BC/BE in a primary care specialty. Excellent compensation including fee-for-service, administrative compensation, and performance bonus. Please reply to Nanette Peter, Associated Emergency Physicians, Inc, 1625 The Alameda, Ste 201, San Jose, CA 95126; (408) 293-8881.

BC/BE PEDIATRICIAN WANTED for semi-rural community 25 miles south of San Francisco to associate with five member Family Practice group. Send inquiry with CV to Lawrence Bruguera, MD, Coastside Medical Clinic, 225 S. Cabrillo Hwy, Ste 100-A, Half Moon Bay, CA 94019; (415) 726-0211.

COASTSIDE MEDICAL CLINIC. BC/BE Family Practitioner wanted for semi-rural community only 25 miles south of San Francisco with five member Family Practic group. Send inquiry and CV to Lawrence Bruguera, MD, 225 S. Cabrillo Hwy, Ste 100-A, Half Moon Bay, CA 94019; (415) 726-0211.

GENERAL ORTHOPAEDIC SURGEON. Position for a BC/BE Orthopaedic Surgeon with a multispecialty 54 physician group practice. Experience must include partial and complete joint replacement. Join a practice with an established growth pattern in community of 120,000 plus, 40 minutes from downtown Sacramento. Marysville Medical Group was founded in 1938 and is the largest private practice group in rural northern California owned and governed by its own physicians. Send CV to Warren J. Boyer, MD, Medical Director, Marysville Medical Group, 800 Third St, Marysville, CA 95901.

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PHYSICIANS WANTED

AMERICAN COLLEGE OF PHYSICIANS
ASSOCIATE EXECUTIVE VICE PRESIDENT HEALTH AND PUBLIC POLICY

The American College of Physicians invites nominations and applications for position of Associate Executive Vice President, Health and Public Policy.

Candidates shall have an MD degree and extensive experience in medicine, research, and public policy. Specialization in Internal Medicine is preferred but not mandatory. Skills in management and administration are essential. Position requires the identification, implementation, and representation of public, scientific, and health policy positions, programs, and research activities taken by the College. Individual will serve as a staff officer of the College, reporting directly to the Executive Vice President and responsible for staff support to the College's Health and Public Policy committees and subcommittees. Deadline for applications is September 14, 1990. Appointment anticipated to begin as early as January 1991. Send detailed CV to:

American College of Physicians
Independence Mall West
Sixth Street at Race
Philadelphia, PA 19106-1572
Attn: AEVP/HPP Search Committee

BC RADIOLOGIST. Position with a multispecialty 54 physician group practice—no hospital. Expertise in conventional diagnostic radiology, ultrasound, mammography, nuclear medicine, CAT, and uroradiology. Three Radiologists, with a staff of 14, do approximately 55,000 procedures annually. Marysville Medical Group was founded in 1938 and is the largest private practice group in rural northern California owned and governed by its own physicians. Send CV to Warren J. Boyer, MD, Medical Director, Marysville Medical Group, 800 Third St, Marysville, CA 95901.

GASTROENTEROLOGIST. Position for a BC/BE gastroenterologist with a multispecialty 54 physician group practice. Certified endoscopy unit and complete in-house radiology and nuclear medicine. Join a practice with an established growth pattern in community of 120,000 plus. Marysville Medical Group was founded in 1938 and is the largest private practice group in rural northern California owned and governed by its own physicians. Send CV to Warren J. Boyer, MD, Medical Director, Marysville Medical Group, 800 Third St, Marysville, CA 95901.

OB/GYN—BC/BE. Position with a multispecialty 54 physician group practice. Join five BC OB/GYN physicians in a practice with an established growth pattern in community of 120,000 plus. Marysville Medical Group was founded in 1938 and is the largest private practice group in rural northern California, owned and governed by its own physicians. Send CV to Warren J. Boyer, MD, Medical Director, Marysville Medical Group, 800 Third St, Marysville, CA 95901.

EXCELLENT OPPORTUNITY for energetic, personable Internist, BC/BE, to assume established practice in eight physician Internal Medicine group in family oriented residential community on San Francisco Bay. Convenient to community hospital; opportunity for teaching appointment. Practice includes EKG reading and once weekly night call plus rapid advancement to full partnership and above average remuneration. Contact Barbara Schneider, Manager, Alameda Medical Group, 501 South Shore Center W, Alameda, CA 94501; (415) 521-2025.

PHYSICIANS WANTED

CALIFORNIA, NORTHERN. A stable group of four ABEM certified/eligible MDs at coastal hospital of 24,000 patient visits would like two new associates. Income $60-$75 per hour. Will consider Family Practice but prefer Emergency Department trained Emergency Physician. Coastal paradise near redwood national parks, minutes from Klamath, Rogue, and Smith Rivers. Video tape of area available. Send CV to EPMG, 120 Montgomery St, Ste 1000, San Francisco, CA 94104.

ATTENTION PHYSICIANS

FHFA IS RECRUITING FOR:
- MEDICAL DIRECTOR
- OB / GYN
- FAMILY PRACTICE
- INTERNAL MEDICINE
- PEDIATRICS

We Offer:
Competitive Salaries
Malpractice Coverage
21 Personal Days Off With Pay
10.5 Paid Holidays
5 Paid Days For C.M.E., Including Allowance For Related Conferences or Seminars
Medical, Dental, Vision Care, Disability And Life Insurance
Eligible to participate in tax deferred savings plan

FHFA is a network of five community health care clinics that provide a broad range of services

Our Clinics are located in San Jose with exceptional cultural / recreational activities.

For more information call (408) 262-7944 ext. 233 or write to:

Bertha Rodriguez, MPH
FHFA
P.O. Box 30051
San Jose, CA 95156-9985

OCCUPATIONAL MEDICINE PHYSICIANS
SANDIA NATIONAL LABORATORIES

Sandia National Laboratories is a research and development laboratory with principal sites in Albuquerque, New Mexico, and Livermore, California. The Laboratories' medical organizations provide a wide variety of services to their employees, including occupational health care, emergency care, and health promotion activities. Full-time physicians BC/BE are being sought for both locations. Experience in an Occupational Medicine setting is desirable. Salary is commensurate with experience and includes a competitive fringe benefit package.

Albuquerque, New Mexico

The Albuquerque area employs 7,500 employees. The medical organization is staffed by five physicians as well as administrative and support personnel. The department is seeking two full-time physicians BC/BE in Preventive Medicine or primary care specialty. Experience in occupational settings and an interest in preventive health care and emergency preparedness is desirable. Physicians will be asked to interact on a regular basis with administrative staff in areas of sickness absence and workers' compensation and with counseling staff for problems associated with psychiatric disorders and chemical dependency. Any interested physicians should send a résumé and three professional references to **Shannon Lytle, Staff Recruiting Coordinator, Division 3531-35, Sandia National Laboratories, PO Box 5800, Albuquerque, NM 87185.**

Livermore, California

The Livermore site employs 1,040 employees. The medical functions reside within the Employee Services Division. A full-time occupational physician with primary care background is required to perform the functions of staff physician, oversee operation of the medical clinc (three nurses and one receptionist), and provide professional medical expertise to management and staff as needed. The abilities to supervise clinic nursing and clerical staff and to work with administrative staff in the areas of workers' compensation and health promotion, and with counseling staff on problems of psychiatric disorders and chemical dependency, are required. Any interested physician should send a résumé and three professional references to **Jim Argyle, Staff Recruiting Coordinator, Division 8522-35, Sandia National Laboratories, PO Box 969, Livermore, CA 94551.**

PHYSICIANS WANTED

GERIATRICIAN/INTERNIST. We are seeking a BC Internist with Geriatric training or certification to join a group of two to practice Geriatric Medicine, actively participate in a university affiliated teaching program, and assist in program development. Competitive salary and excellent fringe benefits. Send CV to Gary Steinke, MD, Santa Clara Valley Medical Center, 750 S. Bascom Ave, San Jose, CA 95128.

PATHOLOGY RESEARCHER (PEDIATRICS). Conduct research regarding hemoglobin levels in children for CHDP (Child Health and Disability Prevention Program) in two areas (1) Hemoglobin and hematocrit levels based on age, environment, nutritional etc. data. (2) Study cholestrol levels in children with emphasis on parental cholestrol levels, history of diabetes, etc. No treatment of patient involved. Write reports. Rotate work schedule between employer's three local offices. Two years experience, 40 hours per week, $101,650 per year. MD Pathology (Pediatrics) degree required. Job site/interview: Glendale, California. Send this ad and your résumé to: JOB # NOF 623, PO Box 9560, Sacramento, CA 95823-0560, no later than September 8, 1990.

POSITION WANTED

INTERNIST, specialist in Pain Management with 10 years experience as director of large Pain Clinic, wishes to relocate. Reply to Number 216, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

PLACEMENT SERVICES

NURSE PRACTITIONERS, PHYSICIAN ASSISTANTS, NURSE MIDWIVES. We provide the right mid-level professional for your clinical setting. Western Practitioner Resources, Heidi Bourne, RN, Director. (800) 345-5859 or (707) 839-5859.

PRACTICES AVAILABLE

FOR SALE

Nice Family Practice in quaint, attractive building in Redding. Near hospitals, bus, lab and x-ray. Two outpatient surgery rooms with overhead lights. Fireplace, stained glass, high ceiling, and lots of wood lend special atmosphere. Quality clientele. Illness forces sale. Call 9 to 12 or 2 to 5, (916) 246-2606 for more information.

FAMILY PRACTICE, BERKELEY, CALIFORNIA. Growing established practice in beautiful San Francisco bay area shared with one associate. Modest buy-in. (415) 843-4544.

ALLERGY-CLINICAL IMMUNOLOGY. Retiring by year's end. Established 40 years. Skin and original blood tests for solving clinical failures both non and immune cases due to food, liquids, oils, dyes, chemicals, medication, vitamins, inhalants, pollen, etc. Many cases are headaches, joint pain, skin, asthma, depression. Diabetics reduce blood sugar about one half, even lupus and M.S. regress. Trained staff. Total price is equal to equipment. Also have been teaching course one or two weeks. 233-D, 550 W. Thomas Rd, Phoenix, AZ 85013.

DON'T FORGET!

The deadline for submitting classifieds for the October issue of WJM is August 27. Send your advertisement to:

Classified Advertising
WJM, PO Box 7602
San Francisco, CA 94120-7602

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PRACTICES AVAILABLE

INTERNAL MEDICINE—San Diego City, high development area. Gross $160,000. Low overhead with high net cash flow. Contact Practice Consultants. (619) 528-2321, Dr Bernard Press, Broker.

SAN DIEGO COUNTY. Cardiology, Internal, OB/GYN and Pediatric practices available. Long established—doctors retiring. Various prices and low down payments. Call CBI, San Diego County's professional practice sales specialists, (619) 283-7009.

SAN FRANCISCO BAY AREA. Pain management practice. Excellent staff and administration. Opportunity for Internist, Psychiatrist, Family Practitioner, Neurologist, or partnership interested in pain or psychosomatic medicine. Reply to Number 208, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

PHYSICIAN OPENING. Small suite to be vacated soon. Building has adjacent physician, specialist, dentist. Great place for young practice. Red Bluff, California; (916) 527-2877.

OB/GYN NORTH HOLLYWOOD—High gross, low overhead. all private patient. Twenty-five year practice. Will refer all OB and major GYN now. To retire December 1991. Room to start now. Call Sandy (805) 524-1013. Nurse will stay.

NORTHERN AND CENTRAL CALIFORNIA. Established practices available: Dermatology, ENT, Family, Internal Medicine, GYN, Ophthalmology, Pediatrics, Personal Injury, Plastic Surgery, Urology. Reasonable terms and prices. Call/write Bradshaw Associates, 21 Altamount, Orinda, CA 94563; (415) 376-0762, FAX (415) 376-0813.

HAYWARD. Fully equipped office for sale or rent to Internist or Pulmonologist. Must agree to continue therapy which has always relieved asthma and COPD during past 30 years. Contact J. J. Robbins, MD, 1634 B St, Hayward, CA 94541; or (415) 581-3451.

OFFICE SPACE

GROWTH AREA OF SANTA CLARA VALLEY. New medical office space for lease in the growth area of Silicon Valley, Morgan Hill, California. Easy access, abundant parking, well located, generous tenant improvement allowances. Excellent patient referral sources. Contact Dr Jon Hatakeyama, (408) 779-7391.

ATTENTION WJM CLASSIFIED ADVERTISERS

The phone extension for WJM classified advertising has been changed to **476.**
The complete number for Classifieds is now (415) 541-0900, ext 476.

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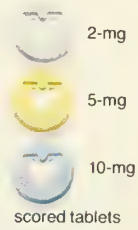

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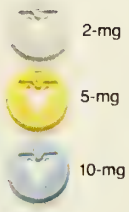

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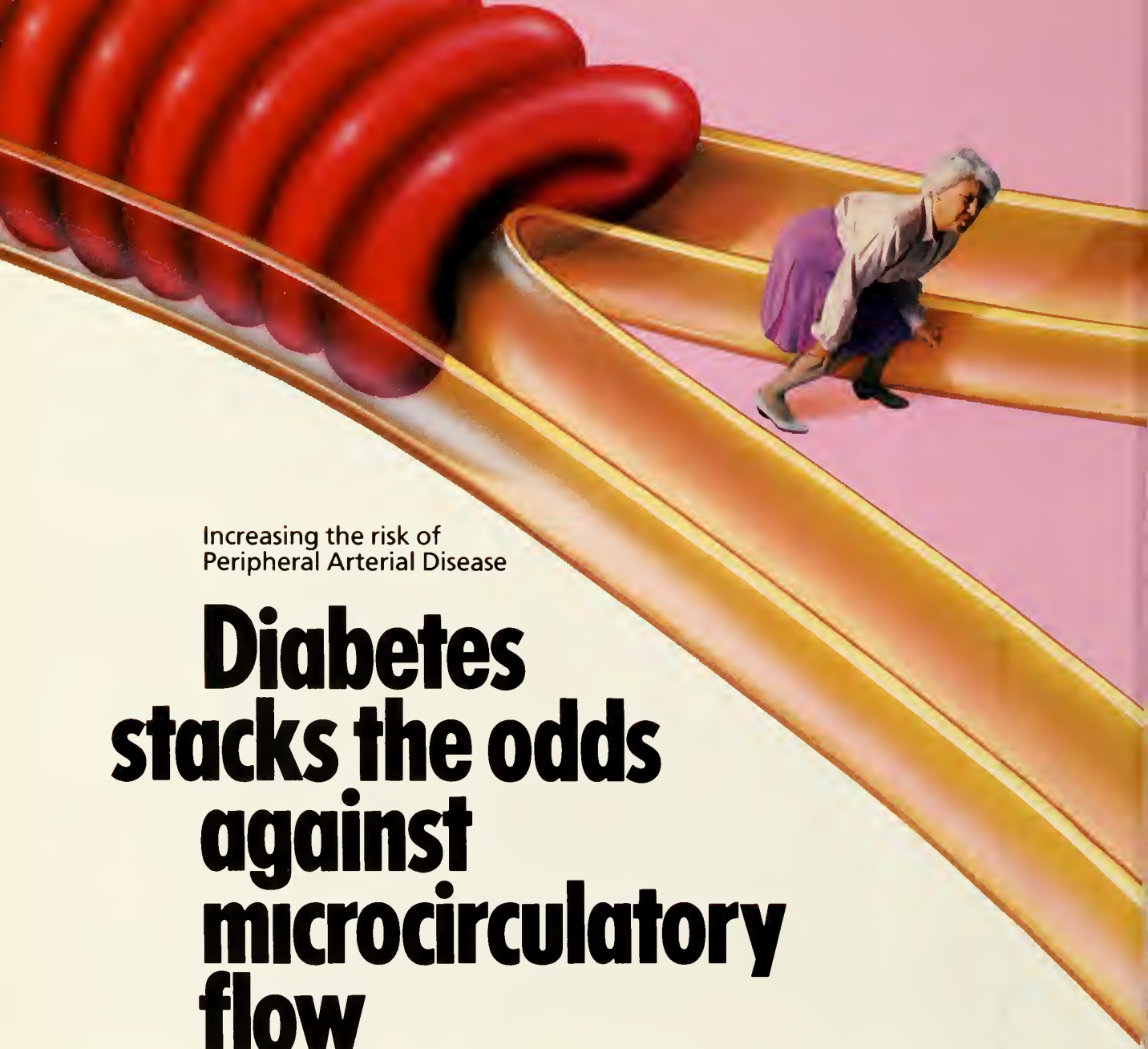

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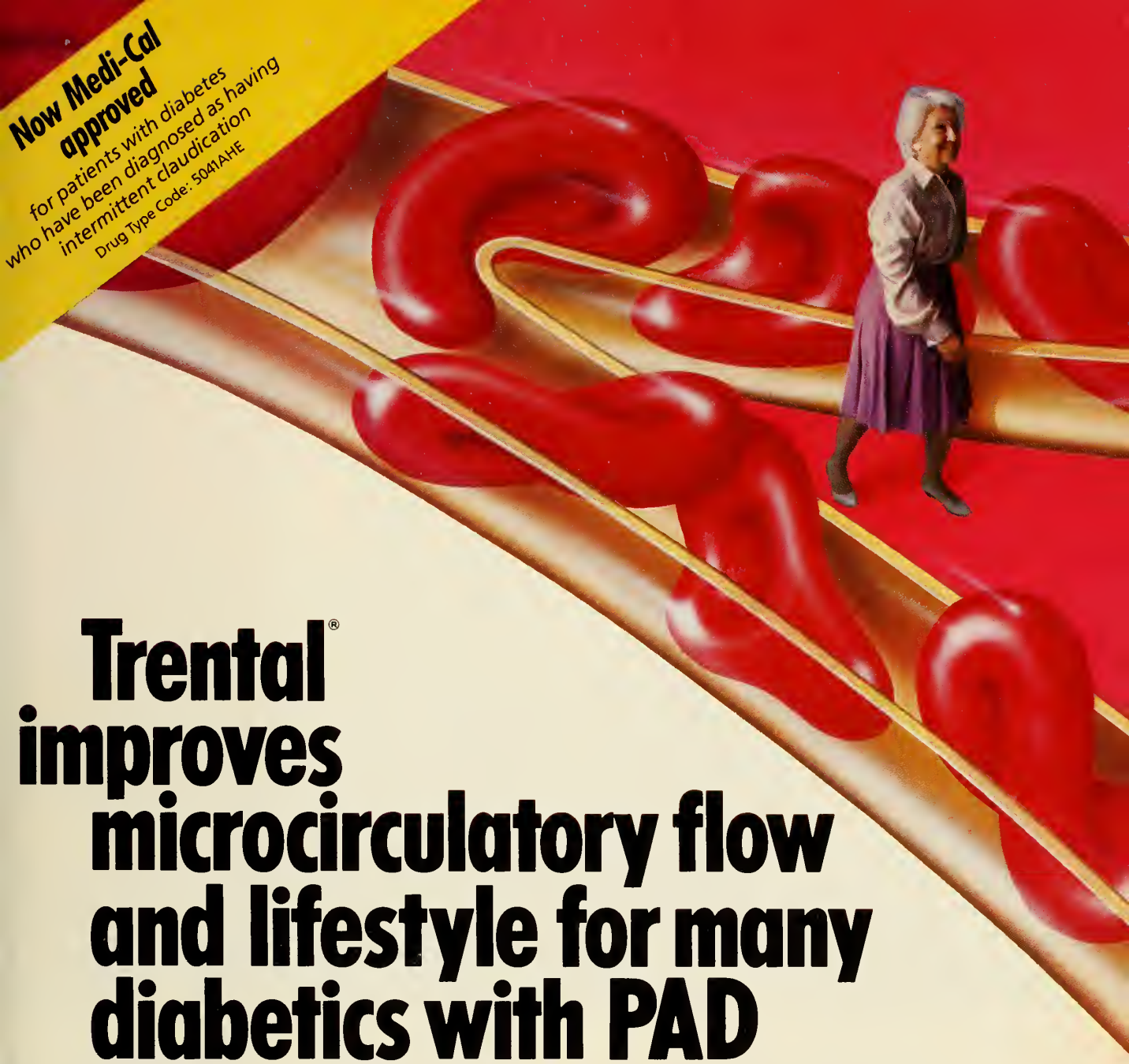

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(ISSN 0093-0415/USPS 084 480) is published monthly for $35 per year (USA and Canada) by the California Medical Association, 221 Main Street, San Francisco, CA 94105. Second-class postage paid at San Francisco and additional mailing offices.

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Retrovir® (zidovudine) significantly delays the onset of AIDS in HIV-infected *asymptomatic* patients (CD4 ≤500 cells/mm^3) ...at 500 mg/day.

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Retrovir significantly delays progression to HIV disease. A recent clinical trial was stopped and patients receiving placebo were offered Retrovir at 500 mg/day.[1]

In a multicenter, placebo-controlled trial carried out in 32 major medical centers, involving 1338 asymptomatic HIV-infected patients (CD4 ≤500 cells/mm^3), RETROVIR was shown to slow HIV disease progression significantly.

The incidence and rates of progression to AIDS in patients receiving RETROVIR at 500 or 1500 mg/day in this trial were less than half those reported with placebo.[1] This significant difference resulted in early termination of the trial and the offering of RETROVIR to patients on placebo.

Patients in this study were monitored for an average of one year. Although treatment of asymptomatic patients delays progression of disease in those patients at risk of progression over the initial 1 to 2 years of treatment, it is not known whether early treatment prolongs survival.

Patients receiving Retrovir were statistically significantly less likely to progress to AIDS.[1]

Treatment Group	Progressions to AIDS	Rate of Progression*
Placebo (n=428)	**33**	**6.6**
RETROVIR 500 mg/day (n=453)	**11**	**2.3**

* Events per 100 person-years of observation.

Changes in immunologic and virologic parameters paralleled the observed clinical benefits.

The recommended daily dose of RETROVIR in asymptomatic patients with CD4 ≤500 cells/mm^3 is 500 mg. This lower dose offers patients efficacy, fewer and less severe adverse events than higher doses, and important cost savings.

Now more than ever, you can do something about HIV infection and disease. It is in your hands to test high-risk patients, monitor patients who test HIV-positive, and treat when appropriate with RETROVIR.

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Retrovir at 500 mg/day is generally well tolerated.*

All reported clinical adverse events were recorded, including those due to underlying infection.

Difference in Adverse Events From Baseline Placebo.

	RETROVIR 500 mg/day (n=453)	Placebo (n=428)	% Difference
Headache	62.5%	52.6%	**9.9%**
Malaise	53.2%	44.9%	**8.3%**
Anorexia	20.1%	10.5%	**9.6%**
Nausea	51.4%	29.9%	**21.5%**
Vomiting	17.2%	9.8%	**7.4%**

* Patients were monitored for tolerance to the study regimens for an average of one year. Difference in adverse events from baseline incidence with placebo (percent of patients). Differences were statistically significant for all events listed.

RETROVIR has been studied in controlled trials in significant numbers of asymptomatic and symptomatic HIV-infected patients, but only for limited periods of time. Therefore, the full safety and efficacy profile of RETROVIR has not been defined, particularly in regard to prolonged use and especially in HIV-infected individuals who have less advanced disease.

Hematologic adverse events with Retrovir in this study were not reported at a statistically significant greater incidence than placebo.[1]

The incidence of hematologic adverse events among asymptomatic patients receiving RETROVIR is lower than would be expected for patients with advanced symptomatic HIV disease.

Although hematologic abnormalities may cause dosing limitations in some patients, temporary dose reductions or interruptions in therapy can help maintain patients on long-term therapy.

The recommended daily dose of RETROVIR in asymptomatic HIV-infected patients (CD4 ≤500 cells/mm^3) is 500 mg since it offers patients efficacy, fewer and less severe adverse events than higher doses, and important cost savings.

Now more than ever, you can do something about HIV infection and disease. It is in your hands to test high-risk patients, monitor patients who test HIV-positive, and treat when appropriate with RETROVIR.

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(zidovudine)
CAPSULES AND SYRUP

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RETROVIR® Capsules
RETROVIR® Syrup
(ZIDOVUDINE)

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Brief Summary

WARNING: THERAPY WITH RETROVIR (ZIDOVUDINE) MAY BE ASSOCIATED WITH HEMATOLOGIC TOXICITY INCLUDING GRANULOCYTOPENIA AND SEVERE ANEMIA REQUIRING TRANSFUSIONS (SEE WARNINGS).

IN ADDITION, PATIENTS TREATED WITH ZIDOVUDINE MAY CONTINUE TO DEVELOP OPPORTUNISTIC INFECTIONS (OI'S) AND OTHER COMPLICATIONS OF HIV INFECTION AND, THEREFORE SHOULD BE UNDER CLOSE CLINICAL OBSERVATION

Microbiology: The development of resistance to zidovudine has not been adequately studied and the frequency of zidovudine-resistant isolates existing in the general population is unknown. Reduced *in vitro* sensitivity to zidovudine has been observed, however, in viral isolates from some individuals who have received prolonged courses of zidovudine treatment. For the small number of patients from whom isolates where studied, no correlations were evident between the development of reduced sensitivity in the laboratory and clinical response. Therefore, the quantitative relationship between *in vitro* susceptibility of HIV to zidovudine and clinical response to therapy has not been established. Studies of the development of resistance to zidovudine are incomplete and the frequency and degree of changes in *in vitro* sensitivity of virus isolates from HIV infected patients with differing severity of immune compromise are unknown.

INDICATIONS AND USAGE: Retrovir is indicated for the management of patients with HIV infection who have evidence of impaired immunity (CD4 cell count of 500/mm³ or less) before therapy is begun.

This indication is based on the results of three randomized, double-blind, placebo-controlled trials of oral zidovudine conducted in the United States, in HIV-infected patients with CD4 counts of 500/mm³ or less. Separate studies evaluated zidovudine therapy in asymptomatic HIV-infected individuals, in patients with early symptomatic HIV disease, and in patients with advanced symptomatic HIV disease (AIDS or advanced ARC).

Asymptomatic HIV Infection: A randomized, double-blind, placebo-controlled trial of oral zidovudine was conducted in asymptomatic, HIV-infected individuals at 32 medical centers. Entry was dependent on the absence of signs and symptoms consistent with HIV disease, such as significant weight loss, fever, diarrhea, secondary infections and evidence of neurological dysfunction. In the study, 1338 asymptomatic individuals with absolute CD4(T4) lymphocyte counts of less than 500 cells/mm³ received a regimen of either 100 mg zidovudine, 300 mg zidovudine, or placebo, each administered five times a day. These study participants were monitored for the development of signs and symptoms of HIV disease and tolerance to the study regimens. The study was terminated early because of a statistically significant difference in progression to advanced symptomatic HIV disease (AIDS or advanced ARC) between the 500 mg/day zidovudine group and the placebo group. Of the 1338 patients enrolled in the study, 38 of the 428 patients receiving placebo, 17 of the 453 individuals receiving 500 mg zidovudine, and 19 of the 457 recipients of 1500 mg zidovudine progressed to advanced symptomatic HIV disease when followed for a mean of 55 weeks (range 19-107 weeks). Of the progressions noted above, AIDS occurred in 33 placebo recipients, 11 individuals receiving 500 mg and 14 patients receiving 1500 mg zidovudine. Changes in immunologic and virologic parameters (ie, CD4[T4] lymphocyte count and serum p24 antigen levels) paralleled the observed clinical benefits. Consistent with various epidemiologic studies of individuals with HIV infection, patients in this study with lower CD4 cell counts or P24 antigenemia were more likely to progress to AIDS. Virtually all patients (for whom data are available) experienced a decline in CD4 cell counts to less than 200 per mm³ before developing an AIDS-defining opportunistic infection. Although treatment of asymptomatic patients delays progression of disease in those patients at risk of progression over the initial 1-2 years of treatment, it is not known whether early treatment prolongs survival.

Zidovudine was well tolerated in a majority of patients. The following adverse clinical events were reported at a significantly greater incidence in individuals receiving 500 mg/day of zidovudine versus placebo: headache, malaise, anorexia, nausea and vomiting (see ADVERSE REACTIONS).

The two most common laboratory abnormalities reported were anemia and granulocytopenia, each of which occurred more often in patients receiving higher doses. These toxicities were easily managed in most cases by temporary dose interruption.

Early Symptomatic HIV Disease: This randomized, double-blind, placebo-controlled trial of oral zidovudine, conducted at 29 medical centers, studied 713 patients with early manifestations of HIV disease (ie, a baseline CD4[T4] cell count of 200 to 800/mm³ and symptoms such as oral thrush, oral hairy leukoplakia or intermittent diarrhea). Patients received either placebo or 200 mg zidovudine every 4 hours (1200 mg/day). The trial was terminated early because of a statistically significant difference in the rates of development of advanced symptomatic HIV disease between the zidovudine and placebo groups. Of the 352 patients receiving placebo, 36 progressed to advanced symptomatic HIV disease, of whom 21 progressed to AIDS, whereas of the 361 zidovudine recipients, 13 progressed to advanced symptomatic HIV disease, of whom 5 progressed to AIDS.

Minimal toxicity was observed. Four percent of zidovudine recipients compared with none of the placebo recipients developed a hemoglobin concentration less than 8 g/dL and 4% of patients treated with zidovudine compared with 1% of placebo recipients developed a granulocyte count less than 750 cells/mm³. Asthenia, dyspepsia, nausea, and vomiting were the major adverse clinical events reported at significantly greater incidences in patients receiving zidovudine.

Advanced Symptomatic HIV Disease: This randomized, double-blind, placebo-controlled trial, conducted at 12 medical centers, was the original trial upon which the marketing of Retrovir was based. In this trial, 281 patients with advanced symptomatic HIV infection including AIDS were studied for a mean of four and a half months.

The patient population of this controlled trial consisted of 160 patients with AIDS (85 Retrovir and 75 placebo) who had recovered from their first episode of PCP diagnosed within the previous four months and 121 patients with ARC (59 Retrovir and 62 placebo) with multiple signs and symptoms of HIV infection, including mucocutaneous candidiasis and/or unexplained weight loss (≥ 15 lbs or >10% of prior body weight). All patients had evidence of impaired cellular immunity with an absence of delayed cutaneous hypersensitivity and CD4 (T4) lymphocytes less than 500 cells/mm³. All patients began therapy at a dose of 250 mg every 4 hours around the clock. This dosage was reduced or temporarily or permanently discontinued after serious marrow toxicity occurred. The trial was stopped early because of a statistically significant difference in mortality. There were 19 deaths in the placebo group and 1 in the Retrovir group. All deaths were apparently due to opportunistic infections (OI) or other complications of HIV infection. Treatment duration ranged from 12 weeks to 26 weeks, with a mean and median duration of 17 and 18 weeks, respectively.

Retrovir also significantly reduced the risk of acquiring an AIDS-defining OI in patients after 6 weeks of treatment. In addition, patients who received Retrovir generally did better than the placebo group in terms of several other measures of efficacy including performance level, neuropsychiatric function, maintenance of body weight and the number and severity of symptoms associated with HIV infection. A small, transient increase in mean CD4 (T4) counts was seen in the zidovudine group but the significance of this finding is unclear.

The most significant adverse reaction noted in the study was a depression of formed elements in the peripheral blood, which necessitated dose reduction or drug discontinuation in 34% of patients receiving Retrovir. Patients with lower CD4 counts were more likely to receive transfusions: 41% of Retrovir recipients and 16% of placebo recipients with <200 CD4 lymphocytes at entry were transfused (see ADVERSE REACTIONS). Only one of 30 Retrovir recipients and none of 30 placebo recipients with >200 CD4 lymphocytes required transfusion.

Although mean platelet counts in Retrovir recipients were statistically increased compared to mean baseline values, thrombocytopenia did occur in some patients. Twelve percent (12%) of Retrovir recipients compared to 5% of placebo recipients had >50% decreases from baseline platelet count.

At the conclusion of the placebo-controlled trial, approximately 80% of Retrovir and placebo recipients elected to enroll in an uncontrolled extension protocol in which all patients received Retrovir at a dose of 200 mg every four hours. This dose was chosen because of concern about hematologic toxicity and to allow for greater flexibility in dosing. These patients have been followed for variable periods of time. As the follow-up period lengthened, patient tracking became increasingly difficult. The intended treatment period of the original study was six months; however, some follow-up data are available for over 90% of patients originally enrolled in the trial. Data from patients in this and other studies show no new or unexpected clinical or laboratory adverse experiences for patients receiving Retrovir other than those listed (see ADVERSE REACTIONS), nor have previously reported adverse events increased significantly in frequency or severity with prolonged drug administration. At any time on study, approximately half of the patients received the recommended dose of zidovudine, while the remaining patients required reduction or interruption of their dosage regimen in response to myelosuppression and/or other clinical adverse events.

Benefits of therapy with Retrovir were observed during this extended period, although opportunistic infections continued to occur and additional patients died. Survival for all patients originally randomized to receive Retrovir was 96.5% at six months, 84.7% at one year, 68.3% at 18 months and 41.2% at two years. One year and two year survival for patients who entered the trial with AIDS was 79% and 31% when calculated since initiation of therapy (87% and 43%, respectively, since the first diagnosis of PCP). These survival rates were determined by the "intention to treat" method, which assumes all patients assigned to a drug actually took the drug throughout the study period.

While a direct comparison with survival data from other cohorts is not possible, untreated patients with AIDS diagnosed in San Francisco in 1985 who had survived 60 days after PCP had a one year survival of 34.7% and a two year survival of 4.2% from diagnosis of PCP. In a recent epidemiologic study of patients with AIDS diagnosed in San Francisco in 1986 and 1987, median survival was improved for patients receiving Retrovir compared to those not receiving therapy with Retrovir (21.6 vs 14.9 months). Actual survival of untreated patients is likely to be lower than reported because of the difficulty in complete ascertainment of mortality. Caution is advised in making comparisons from such "natural history" experience since case definitions and follow-up practices vary.

Other, uncontrolled studies have shown that Retrovir (zidovudine) may be of benefit in treating women, intravenous drug users, and racial minorities, in addition to the patient population (primarily white males) included in the controlled trials.

Dose Comparison Study: Results from a randomized, unblinded, dose comparison study of zidovudine, in patients with AIDS who had experienced an episode of PCP, indicate that an induction dose of zidovudine 200 mg administered orally every four hours (1200 mg/day) for one month, followed by chronic administration of 100 mg every 4 hours (600 mg/day), was associated with survival rates and frequency of opportunistic infections comparable to those observed in patients administered higher dosages as tolerated. The 600 mg per day regimen was also associated with a lower incidence of hematologic toxicity. The effectiveness of this lower dose in improving the neurologic dysfunction associated with HIV disease, however, is unknown (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS: Retrovir Capsules and Syrup are contraindicated for patients who have potentially life-threatening allergic reactions to any of the components of the formulations.

WARNINGS: Zidovudine has been studied in controlled trials in significant numbers of asymptomatic and symptomatic HIV infected patients, but only for limited periods of time. Therefore, the full safety and efficacy profile of zidovudine has not been defined, particularly in regard to prolonged use and especially in HIV infected individuals who have less advanced disease (see following sections for more specific information: INDICATIONS AND USAGE, Microbiology, Carcinogenesis, Mutagenesis, Impairment of Fertility).

Zidovudine should be used with extreme caution in patients who have bone marrow compromise evidenced by granulocyte count <1000/mm³ or hemoglobin <9.5 g/dL. In all of the placebo-controlled studies, but most frequently in patients with advanced symptomatic HIV disease, anemia and granulocytopenia were the most significant adverse events observed (see ADVERSE REACTIONS). There have been reports of pancytopenia associated with the use of zidovudine, which was reversible in most instances after discontinuance of the drug.

Significant anemia most commonly occurred after 4 to 6 weeks of therapy and in many cases required dose adjustment, discontinuation of zidovudine, and/or blood transfusions. Frequent blood counts are strongly recommended in patients with advanced HIV disease taking zidovudine. For asymptomatic HIV-infected individuals and patients with early HIV disease, most of whom have better marrow reserve, blood counts may be obtained less frequently, depending upon the patient's overall status. If anemia or granulocytopenia develops, dosage adjustments may be necessary (see DOSAGE AND ADMINISTRATION).

Sensitization reactions, including anaphylaxis in one patient, have been reported in individuals receiving zidovudine therapy. Patients experiencing a rash should undergo medical evaluation.

Coadministration of zidovudine with other drugs metabolized by glucuronidation should be avoided because the toxicity of either drug may be potentiated (see Drug Interactions under PRECAUTIONS). Zidovudine recipients who used acetaminophen during the controlled trial in advance HIV disease, had an increased incidence of granulocytopenia which appeared to be correlated with the duration of acetaminophen use.

PRECAUTIONS:

General: Zidovudine is eliminated from the body primarily by renal excretion following metabolism in the liver (glucuronidation). There are currently very little data available concerning the use of zidovudine in patients with impaired renal function (see Pharmacokinetics subsection of CLINICAL PHARMACOLOGY) and no data in patients with impaired hepatic function. These patients may be at greater risk of toxicity from zidovudine.

Information for Patients: See full prescribing information.

Drug Interactions: The interaction of other drugs with zidovudine has not been studied in a systematic manner. Coadministration of zidovudine with drugs that are nephrotoxic, cytotoxic, or which interfere with RBC/WBC number or function (eg, dapsone, pentamidine, amphotericin B, flucytosine, vincristine, vinblastine, adriamycin, or interferon) may increase the risk of toxicity. Limited data suggest that probenecid may inhibit glucuronidation and/or reduce renal excretion of zidovudine. In addition, other drugs (eg, acetaminophen, aspirin, or indomethacin) may competitively inhibit glucuronidation (see WARNINGS). Phenytoin levels have been reported to be low in some patients receiving zidovudine, while in one case a high level was documented. These observations suggest that phenytoin levels should be carefully monitored in patients receiving zidovudine since many patients with advanced HIV infections have CNS conditions which may predispose to seizure activity.

Some experimental nucleoside analogues which are being evaluated in HIV-infected patients may affect RBC/WBC number or function and may increase the potential for hematologic toxicity of zidovudine. Some experimental nucleoside analogues affecting DNA replication antagonize the *in vitro* antiviral activity of zidovudine against HIV and thus, concomitant use of such drugs should be avoided.

Some drugs such as trimethoprim-sulfamethoxazole, pyrimethamine, and acyclovir may be necessary for the management or prevention of opportunistic infections. In the controlled trial, in patients with advanced HIV disease, increased toxicity was not detected with limited exposure to these drugs. However, there is one published report of neurotoxicity (profound lethargy) associated with concomitant use of zidovudine and acyclovir.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Zidovudine was administered orally at three dosage levels to separate groups of mice and rats (60 females and 60 males in each group). Initial single daily doses were 30, 60 and 120 mg/kg/day in mice and 80, 220 and 600 mg/kg/day in rats. The doses in mice were reduced to 20, 30 and 40 mg/kg/day after day 90 because of treatment-related anemia, whereas in rats only the high dose was reduced to 450 mg/kg/day on day 91 and then to 300 mg/kg/day on day 279.

In mice, seven late-appearing (after 19 months) vaginal neoplasms (5 non-metastasizing squamous cell carcinomas, one squamous cell papilloma and one squamous polyp) occurred in animals given the highest dose. One late-appearing squamous cell papilloma occurred in the vagina of a middle dose animal. No vaginal tumors were found at the lowest dose.

In rats, two late-appearing (after 20 months), non-metastasizing vaginal squamous cell carcinomas occurred in animals given the highest dose. No vaginal tumors occurred at the low or middle dose in rats.

No other drug-related tumors were observed in either sex of either species.

It is not known how predictive the results of rodent carcinogenicity studies may be for man. At doses that produced tumors in mice and rats, the estimated drug exposure (as measured by AUC) was approximately 3 times (mouse) and 24 times (rat) the estimated human exposure at the recommended therapeutic dose of 100 mg every 4 hours.

No evidence of mutagenicity (with or without metabolic activation) was observed in the Ames *Salmonella* mutagenicity assay. In a mutagenicity assay conducted in L5178Y/TK$^{+/-}$ mouse lymphoma cells, zidovudine was weakly mutagenic in the absence of metabolic activation only at the highest concentrations tested (4000 and 5000 μg/mL). In the presence of metabolic activation, the drug was weakly mutagenic at concentrations of 1000 μg/mL and higher. In an *in vitro* mammalian cell transformation assay, zidovudine was positive at concentrations of 0.5 μg/mL and higher. In an *in vitro* cytogenetic study performed in cultured human lymphocytes, zidovudine induced dose-related structural chromosomal abnormalities at concentrations of 3 μg/mL and higher. No such effects were noted at the two lowest concentrations tested, 0.3 and 1 μg/mL. In an *in vivo* cytogenetic study in rats given a single intravenous injection of zidovudine at doses of 37.5 to 300 mg/kg, there were no treatment-related structural or numerical chromosomal alterations in spite of plasma levels that were as high as 453 μg/mL five minutes after dosing.

In two *in vivo* micronucleus studies (designed to measure chromosome breakage or mitotic spindle apparatus damage) in male mice, oral doses of zidovudine of 100 to 1000 mg/kg/day administered once daily for approximately 4 weeks induced dose-related increases in micronucleated erythrocytes. Similar results were also seen after 4 or 7 days of dosing at 500 mg/kg/day in rats and mice.

No effect on male or female fertility (judged by conception rates) was seen in rats given zidovudine orally at doses up to 450 mg/kg/day.

Pregnancy: Pregnancy Category C. Oral teratology studies in the rat and in the rabbit at doses up to 500 mg/kg/day revealed no evidence of teratogenicity with zidovudine. The incidence of fetal resorptions was increased in rats given 150 or 450 mg/kg/day and rabbits given 500 mg/kg/day. The doses used in the teratology studies resulted in peak plasma concentrations in rats of 68 to 234 times the peak human plasma concentrations and in rabbits of 14 to 90 times the peak human plasma concentrations. It is not known whether zidovudine can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Zidovudine should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether zidovudine is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions from zidovudine in nursing infants, mothers should be instructed to discontinue nursing if they are receiving zidovudine.

Pediatric Use: The effectiveness of zidovudine in patients 12 years and younger has not been confirmed. Experience from Phase 1 studies shows that zidovudine administered orally at doses of 120 to 180 mg/m² every six hours (480 to 720 mg/m² per day) appears to give a side effect profile similar to adults. Overall, the pharma-

cokinetics of zidovudine in children, 6 months through 12 years of age, are similar to those observed in adult patients.

ADVERSE REACTIONS: The frequency and severity of adverse events associated with the use of zidovudine are greater in patients with more advanced infection at the time of initiation of therapy. The following tables summarize the relative incidence of hematologic adverse events observed in the placebo-controlled clinical studies by severity of HIV disease present at the start of treatment

Asymptomatic HIV Infection Study (n=1338)	Granulocytopenia (<750/mm³)			Anemia (Hgb<8 g/dL)		
	Zidovudine		Placebo	Zidovudine		Placebo
	1500 mg*	500 mg		1500 mg*	500 mg	
C04 ≤ 500	6.4% (n=457)	1.8% (n=453)	1.6% (n=428)	6.4% (n=457)	1.1% (n=453)	0.2% (n=428)

Early Symptomatic HIV Disease Study (n=713)	Granulocytopenia (<750/mm³)		Anemia (Hgb<8 g/dL)	
	Zidovudine 1200 mg	Placebo	Zidovudine 1200 mg	Placebo
C04>200	4%(n=361)	1%(n=352)	4%(n=361)	0%(n=352)

Advanced Symptomatic HIV Disease Study (n=281)	Granulocytopenia (<750/mm³)		Anemia (Hgb<7.5 g/dL)	
	Zidovudine 1500 mg*	Placebo	Zidovudine 1500 mg*	Placebo
C04>200	10%(n=30)	3%(n=30)	3%(n=30)	0%(n=30)
C04<200	47%(n=114)	10%(n=107)	29%(n=114)	5%(n=107)

*Three times the currently recommended dose in asymptomatic patients.

The anemia reported in patients receiving zidovudine appeared to be the result of impaired erythrocyte maturation as evidenced by increased macrocytosis (MCV) while on drug.

The HIV-infected individuals participating in these clinical trials often had baseline symptoms and signs of HIV disease and/or experienced adverse events at some time during study. It was often difficult to distinguish adverse events possibly associated with zidovudine administration from underlying signs of HIV disease or intercurrent illnesses. The following table summarizes clinical adverse events or symptoms which occurred in at least 5% of all patients with advanced HIV disease treated with zidovudine in the original placebo-controlled study. Of the items listed in the table, only severe headache, nausea, insomnia and myalgia were reported at a significantly greater rate in zidovudine recipients.

Percentage (%) of Patients with Clinical Events in the Advanced HIV Disease Study

Adverse Event	Zidovudine (n=144) %	Placebo (n=137) %	Adverse Event	Zidovudine (n=144) %	Placebo (n=137) %
BODY AS A WHOLE			MUSCULOSKELETAL		
Asthenia	19	18	Myalgia	8	2
Diaphoresis	5	4	NERVOUS		
Fever	16	12	Dizziness	6	4
Headache	42	37	Insomnia	5	1
Malaise	8	7	Paresthesia	6	3
GASTROINTESTINAL			Somnolence	8	9
Anorexia	11	8	RESPIRATORY		
Diarrhea	12	18	Dyspnea	5	3
Dyspepsia	5	4	SKIN		
GI Pain	20	19	Rash	17	15
Nausea	46	18	SPECIAL SENSES		
Vomiting	6	3	Taste Perversion	5	8

Clinical adverse events which occurred in less than 5% of all patients treated with zidovudine in the advanced HIV study are listed below. Since many of these adverse events were seen in placebo-treated patients as well as zidovudine recipients, their possible relationship to the drug is unknown.

Body as a whole: body odor, chills, edema of the lip, flu syndrome, hyperalgesia, back pain, chest pain, lymphadenopathy.

Cardiovascular: vasodilation.

Gastrointestinal: constipation, dysphagia, edema of the tongue, eructation, flatulence, bleeding gums, rectal hemorrhage, mouth ulcer.

Musculoskeletal: arthralgia, muscle spasm, tremor, twitch.

Nervous: anxiety, confusion, depression, emotional lability, nervousness, syncope, loss of mental acuity, vertigo.

Respiratory: cough, epistaxis, pharyngitis, rhinitis, sinusitis, hoarseness.

Skin: acne, pruritus, urticaria.

Special senses: amblyopia, hearing loss, photophobia.

Urogenital: dysuria, polyuria, urinary frequency, urinary hesitancy.

Subsequent to the initial trial, sensitization reactions, including anaphylaxis in one patient, have been reported in individuals receiving zidovudine therapy.

All unexpected events and expected events of a severe or life-threatening nature were monitored in the placebo-controlled studies in early HIV disease and asymptomatic HIV infection. Data concerning the occurrence of additional signs or symptoms were also collected. No distinction was made in reporting events between those possibly associated with the administration of the study medication and those due to the underlying disease. The following tables summarize all those events reported at a statistically significant greater incidence for zidovudine recipients in these studies:

Percentage (%) of Patients with Clinical Events in the Early Symptomatic HIV Disease Study

Adverse Event	Zidovudine (n=361) %	Placebo (n=352) %
BODY AS A WHOLE		
Asthenia	69	62
GASTROINTESTINAL		
Dyspepsia	6	1
Nausea	61	41
Vomiting	25	13

Percentage (%) of Patients with Clinical Events* in an Asymptomatic HIV Infection Study

Adverse Event	1500 mg Zidovudine*** (n=457) %	500 mg Zidovudine (n=453) %	Placebo (n=428) %
BODY AS A WHOLE			
Asthenia	10.1	8.6**	5.8
Headache	58.0**	62.5	52.6
Malaise	55.6	53.2	44.9
GASTROINTESTINAL			
Anorexia	19.3	20.1	10.5
Constipation	8.1	6.4**	3.5
Nausea	57.3	51.4	29.9
Vomiting	16.4	17.2	9.8
NERVOUS			
Dizziness	20.8	17.9**	15.2

*Reported in ≥ 5% of study population.
**Not statistically significant versus placebo.
***Three times the currently recommended dose in asymptomatic patients.

The following events have been reported in patients treated with zidovudine: seizures, myopathy, nail pigmentation, changes in liver function tests. They may also occur as part of the underlying disease process. As such, the relationship between these events and the use of zidovudine is uncertain.

U.S. Patent No. 4724232 (Use Patent)
Other Pats. Pending

Wellcome
Burroughs Wellcome Co.
Research Triangle Park, NC 27709

Reference: 1. Volberding PA, Lagakos SW, Koch MA, et al. Zidovudine in asymptomatic human immunodeficiency virus infection: a controlled trial in persons with fewer than 500 CD4-positive cells per cubic millimeter. *N Engl J Med.* 1990;322:941-949.

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RT111

RETROVIR®
(zidovudine)
CAPSULES AND SYRUP

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Minimal potential for drug interactions

Unlike cimetidine and ranitidine,[1] Axid does not inhibit the cytochrome P-450 metabolizing enzyme system.[2]

Swift and effective H_2-antagonist therapy

- *Most patients experience pain relief with the first dose[3]*
- *Heals duodenal ulcer rapidly and effectively[4,5]*
- *Dosage for adults with active duodenal ulcer is 300 mg once nightly (150 mg b.i.d. is also available)*

References

1. USP DI Update, September/October 1988, p 120.
2. Br J Clin Pharmacol 1985;20:710-713.
3. Data on file, Lilly Research Laboratories.
4. Scand J Gastroenterol 1987;22(suppl 136):61-70.
5. Am J Gastroenterol 1989;84:769-774.

AXID®
nizatidine capsules

Brief Summary. Consult the package literature for complete information.

Indications and Usage: 1. *Active duodenal ulcer*—for up to eight weeks of treatment. Most patients heal within four weeks.

2. *Maintenance therapy*—for healed duodenal ulcer patients at a reduced dosage of 150 mg h.s. The consequences of therapy with Axid for longer than one year are not known.

Contraindication: Known hypersensitivity to the drug. Use with caution in patients with hypersensitivity to other H_2-receptor antagonists.

Precautions: *General*—1. Symptomatic response to nizatidine therapy does not preclude the presence of gastric malignancy.

2. Dosage should be reduced in patients with moderate to severe renal insufficiency.

3. In patients with normal renal function and uncomplicated hepatic dysfunction, the disposition of nizatidine is similar to that in normal subjects.

Laboratory Tests—False-positive tests for urobilinogen with Multistix® may occur during therapy.

Drug Interactions—No interactions have been observed with theophylline, chlordiazepoxide, lorazepam, lidocaine, phenytoin, and warfarin. Axid does not inhibit the cytochrome P-450 enzyme system; therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. In patients given very high doses (3,900 mg) of aspirin daily, increased serum salicylate levels were seen when nizatidine, 150 mg b.i.d., was administered concurrently.

Carcinogenesis, Mutagenesis, Impairment of Fertility—A two-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose-related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a two-year study in mice, there was no evidence of a carcinogenic effect in male mice, although hyperplastic nodules of the liver were increased in the high-dose males as compared with placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups. The rate of hepatic carcinoma in the high-dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement as compared with concurrent controls and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery are not considered evidence of a carcinogenic potential for Axid.

Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, mouse lymphoma assay, chromosome aberration tests, and a micronucleus test.

In a two-generation, perinatal and postnatal fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

Pregnancy—Teratogenic Effects—Pregnancy Category C—Oral reproduction studies in rats at doses up to 300 times the human dose and in Dutch Belted rabbits at doses up to 55 times the human dose revealed no evidence of impaired fertility or teratogenic effect; but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights. On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in one fetus, and at 50 mg/kg, it produced ventricular anomaly, distended abdomen, spina bifida, hydrocephaly, and enlarged heart in one fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers—Studies in lactating women have shown that 0.1% of an oral dose is secreted in human milk in proportion to plasma concentrations. Because of growth depression in pups reared by treated lactating rats, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

Pediatric Use—Safety and effectiveness in children have not been established.

Use in Elderly Patients—Healing rates in elderly patients were similar to those in younger age groups as were the rates of adverse events and laboratory test abnormalities. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

Adverse Reactions: Clinical trials of varying durations included almost 5,000 patients. Among the more common adverse events in domestic placebo-controlled trials of over 1,900 nizatidine patients and over 1,300 on placebo, sweating (1% vs 0.2%), urticaria (0.5% vs <0.01%), and somnolence (2.4% vs 1.3%) were significantly more common with nizatidine. It was not possible to determine whether a variety of less common events was due to the drug.

Hepatic—Hepatocellular injury (elevated liver enzyme tests or alkaline phosphatase) possibly or probably related to nizatidine occurred in some patients. In some cases, there was marked elevation (>500 IU/L) in SGOT or SGPT and, in a single instance, SGPT was >2,000 IU/L. The incidence of elevated liver enzymes overall and elevations of up to three times the upper limit of normal, however, did not significantly differ from that in placebo patients. Hepatitis and jaundice have been reported. All abnormalities were reversible after discontinuation of Axid.

Cardiovascular—In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in two individuals administered Axid and in three untreated subjects.

CNS—Rare cases of reversible mental confusion have been reported.

Endocrine—Clinical pharmacology studies and controlled clinical trials showed no evidence of antiandrogenic activity due to nizatidine. Impotence and decreased libido were reported with equal frequency by patients on nizatidine and those on placebo. Gynecomastia has been reported rarely.

Hematologic—Fatal thrombocytopenia was reported in a patient treated with nizatidine and another H_2-receptor antagonist. This patient had previously experienced thrombocytopenia while taking other drugs. Rare cases of thrombocytopenic purpura have been reported.

Integumental—Sweating and urticaria were reported significantly more frequently in nizatidine- than in placebo-treated patients. Rash and exfoliative dermatitis were also reported.

Hypersensitivity—As with other H_2-receptor antagonists, rare cases of anaphylaxis following nizatidine administration have been reported. Because cross-sensitivity among this class has been observed, H_2-receptor antagonists should not be administered to those with a history of hypersensitivity to these agents. Rare episodes of hypersensitivity reactions (eg, bronchospasm, laryngeal edema, rash, and eosinophilia) have been reported.

Other—Hyperuricemia unassociated with gout or nephrolithiasis was reported. Eosinophilia, fever, and nausea related to nizatidine have been reported.

Overdosage: Overdoses of Axid have been reported rarely. If overdosage occurs, activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. Renal dialysis for four to six hours increased plasma clearance by approximately 84%.

PV 2098 AMP [091289]

Additional information available to the profession on request.

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Indianapolis, Indiana
46285

NZ-2924-B-049310

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Axid® (nizatidine, Lilly)

The Western Journal of Medicine
(ISSN 0093-0415/USPS 084 480) is published monthly for $35 per year (USA and Canada) by the California Medical Association, 221 Main Street, San Francisco, CA 94105. Second-class postage paid at San Francisco, CA and additional mailing offices.
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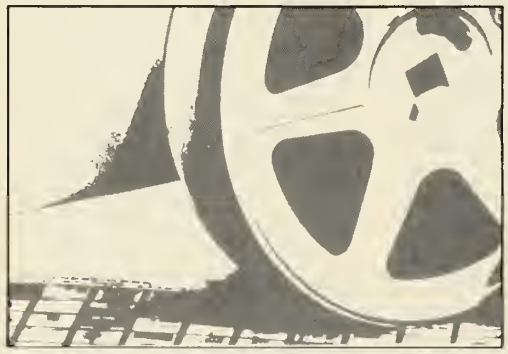

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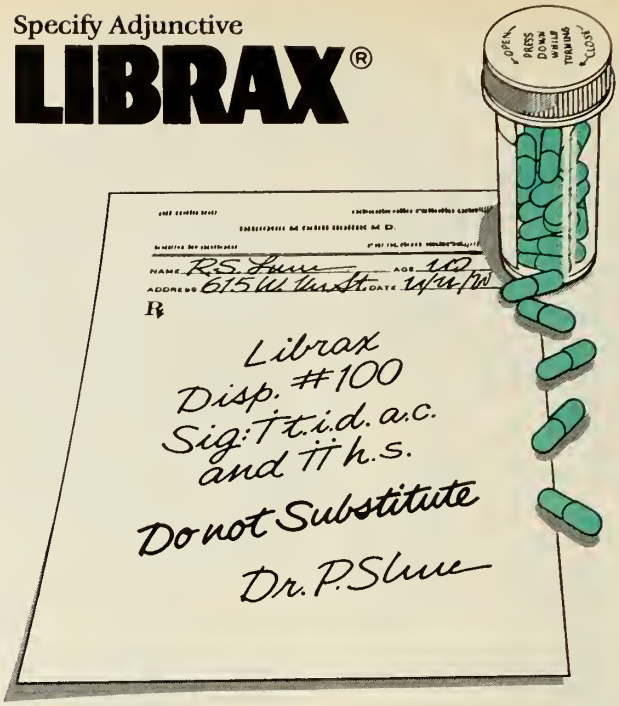

Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium bromide.

Please consult complete prescribing information, a summary of which follows:

* **Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:
"Possibly" effective: as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.
Final classification of the less-than-effective indications requires further investigation.

Contraindications: Glaucoma; prostatic hypertrophy, benign bladder neck obstruction; hypersensitivity to chlordiazepoxide HCl and/or clidinium Br.
Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants, and against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).
Usage in Pregnancy: **Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.**
As with all anticholinergics, inhibition of lactation may occur.
Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).
Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established. Inform patients to consult physician before increasing dose or abruptly discontinuing this drug.
Adverse Reactions: No side effects or manifestations not seen with either compound alone reported with Librax. When chlordiazepoxide HCl is used alone, drowsiness, ataxia, confusion may occur, especially in elderly and debilitated; avoidable in most cases by proper dosage adjustment, but also occasionally observed at lower dosage ranges. Syncope reported in a few instances. Also encountered: isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent, generally controlled with dosage reduction; changes in EEG patterns may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice, hepatic dysfunction reported occasionally with chlordiazepoxide HCl, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax typical of anticholinergic agents, *i.e.*, dryness of mouth, blurring of vision, urinary hesitancy, constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.
Drug Abuse and Dependence: Withdrawal symptoms similar to those noted with barbiturates and alcohol have occurred following abrupt discontinuance of chlordiazepoxide; more severe seen after excessive doses over extended periods; milder after taking continuously at therapeutic levels for several months. After extended therapy, avoid abrupt discontinuation and taper dosage. Carefully supervise addiction-prone individuals because of predisposition to habituation and dependence.

P.I. 0288

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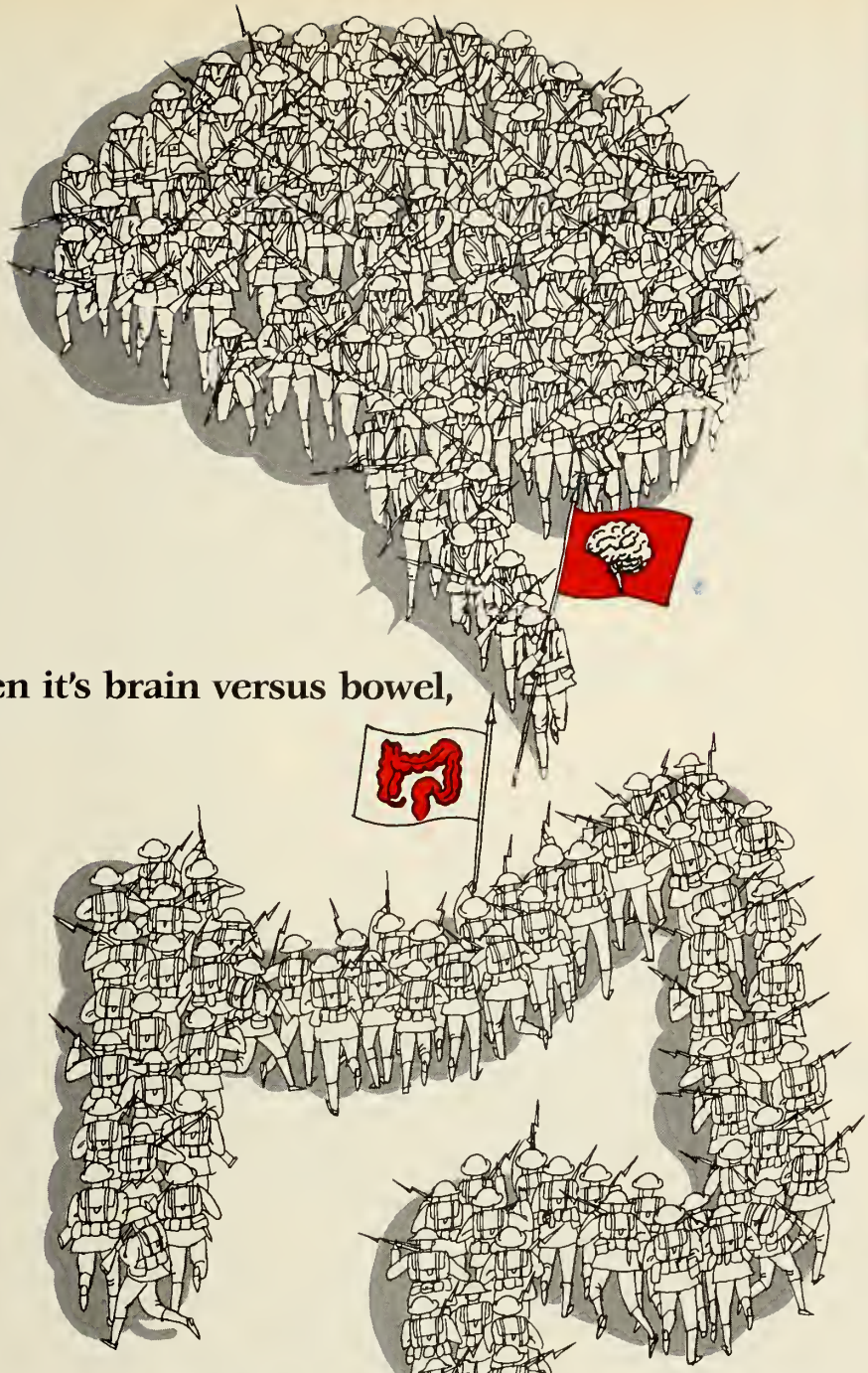

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*Librax has been evaluated as possibly effective as adjunctive therapy in the treatment of peptic ulcer and IBS.

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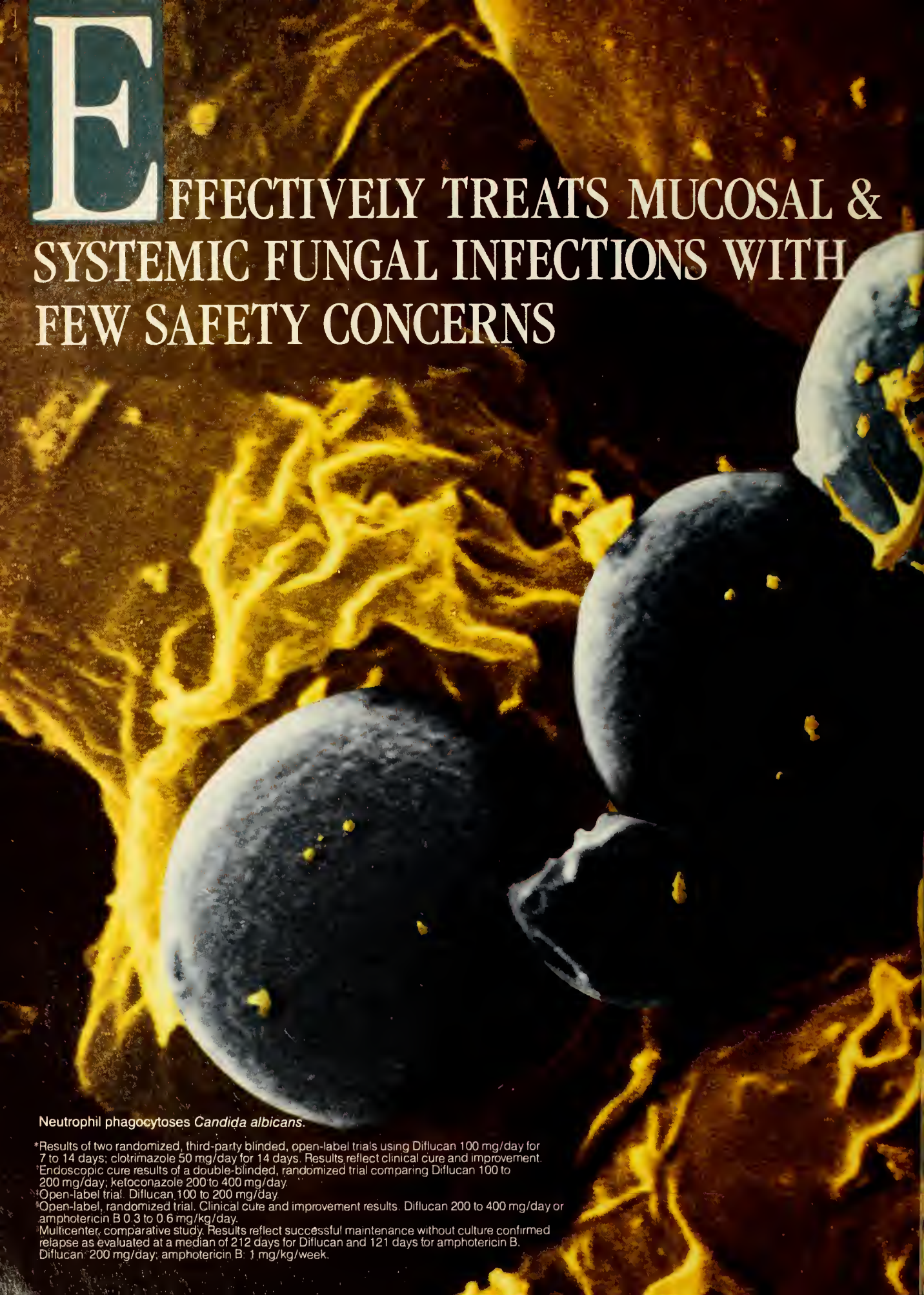
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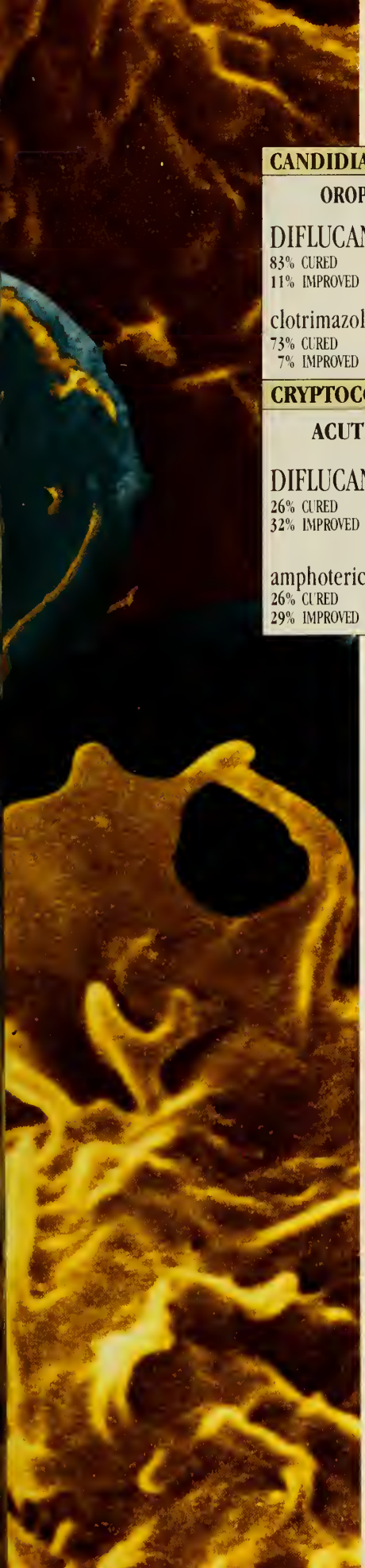
Neutrophil phagocytoses *Candida albicans*.
*Results of two randomized, third-party blinded, open-label trials using Diflucan 100 mg/day for 7 to 14 days; clotrimazole 50 mg/day for 14 days. Results reflect clinical cure and improvement.
†Endoscopic cure results of a double-blinded, randomized trial comparing Diflucan 100 to 200 mg/day; ketoconazole 200 to 400 mg/day.
‡Open-label trial. Diflucan 100 to 200 mg/day.
§Open-label, randomized trial. Clinical cure and improvement results. Diflucan 200 to 400 mg/day or amphotericin B 0.3 to 0.6 mg/kg/day.
¶Multicenter, comparative study. Results reflect successful maintenance without culture confirmed relapse as evaluated at a median of 212 days for Diflucan and 121 days for amphotericin B. Diflucan: 200 mg/day; amphotericin B: 1 mg/kg/week.



Excellent clinical success in oropharyngeal, esophageal, and systemic candidiasis, and cryptococcal meningitis:
Interim results from ongoing studies; due to the interim nature of these studies, statistics have not been provided.

CANDIDIASIS[1*]					
OROPHARYNGEAL[1*]		ESOPHAGEAL[1‡] (endoscopic cures)		SYSTEMIC[1‡]	
DIFLUCAN 83% CURED 11% IMPROVED	94% (61/65)	DIFLUCAN	87% (20/23)	DIFLUCAN 63% CURED 23% IMPROVED	86% (189/219)
clotrimazole 73% CURED 7% IMPROVED	80% (36/45)	ketoconazole	53% (9/17)		

CRYPTOCOCCAL MENINGITIS			
ACUTE THERAPY[1§]		MAINTENANCE TO PREVENT RELAPSE[1‖]	
DIFLUCAN 26% CURED 32% IMPROVED	58% (54/93)	DIFLUCAN	98% (104/106)
amphotericin B 26% CURED 29% IMPROVED	55% (32/58)	amphotericin B	83% (64/77)

Excellent safety profile and patient compliance
In over 4,000 patients who received Diflucan for at least 7 days, the most common adverse events were nausea (3.7%), headaches (1.9%), and skin rash (1.8%).[1]

Rare incidence of serious hepatotoxicity has been reported, but the causal relationship to Diflucan is uncertain.[1]

Penetration to key tissues, organs, and fluids
Distribution throughout the body approximates that of total body water after oral or IV dosing.[1]

Oral bioavailability of Diflucan >90% and unaffected by agents that increase gastric pH.[1]

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ONCE-A-DAY
Diflucan® ORAL / IV
(fluconazole)
100 mg, 200 mg Tablets / 200 mg, 400 mg IV Injection

The Antifungal Effectiveness You Need.
The Safety Profile You Want.

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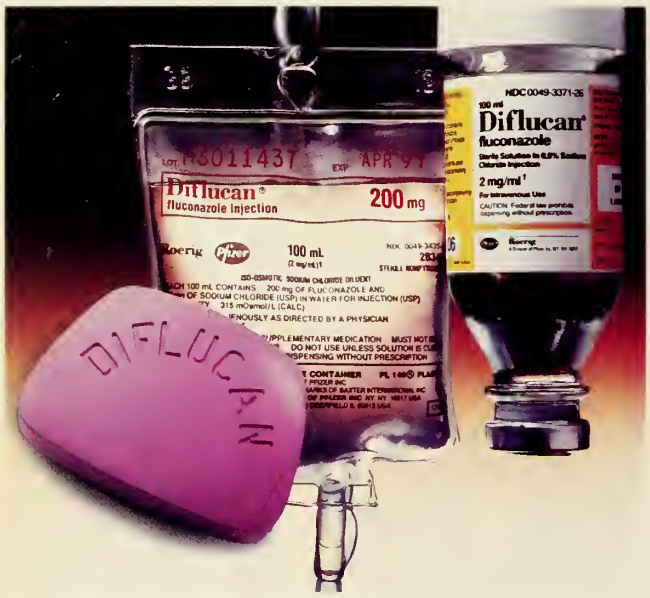

WITH ONCE DAILY DOSING FOR A WIDE RANGE OF PATIENTS

INDICATION	FIRST DAY	DAILY THERAPY	MINIMUM DURATION OF THERAPY
OROPHARYNGEAL CANDIDIASIS:	200 mg	100 mg	14 days
ESOPHAGEAL CANDIDIASIS:	200 mg	100 mg*	21 days
SYSTEMIC CANDIDIASIS:	400 mg	200 mg	28 days
CRYPTOCOCCAL MENINGITIS (acute):	400 mg	200 mg*	10-12 weeks after CSF becomes culture negative
CRYPTOCOCCAL MENINGITIS (maintenance to prevent relapse):	200 mg	200 mg	

*Doses of up to 400 mg/day may be used based on medical judgement of the patient's response to therapy.

References: 1 Data on file, Roerig division of Pfizer Pharmaceuticals

INDICATIONS AND USAGE

DIFLUCAN (fluconazole) is indicated for the treatment of

1 Dropharyngeal and esophageal candidiasis DIFLUCAN is also effective for the treatment of serious systemic candidal infections, including urinary tract infection, peritonitis, and pneumonia

2 Cryptococcal meningitis

Specimens for fungal culture and other relevant laboratory studies (serology, histopathology) should be obtained prior to therapy to isolate and identify causative organisms Therapy may be instituted before the results of the cultures and other laboratory studies are known, however, once these results become available, antiinfective therapy should be adjusted accordingly

CONTRAINDICATIONS

DIFLUCAN (fluconazole) is contraindicated in patients who have shown hypersensitivity to fluconazole or to any of its excipients There is no information regarding cross hypersensitivity between fluconazole and other azole antifungal agents Caution should be used in prescribing DIFLUCAN to patients with hypersensitivity to other azoles

WARNINGS

Patients who develop abnormal liver function tests during DIFLUCAN therapy should be monitored for the development of more severe hepatic injury Although serious hepatic reactions have been rare and the causal association with DIFLUCAN uncertain, if clinical signs and symptoms consistent with liver disease develop that may be attributable to fluconazole, DIFLUCAN should be discontinued (See Adverse Reactions)

Immunocompromised patients who develop rashes during treatment with DIFLUCAN should be monitored closely and the drug discontinued if lesions progress (See Adverse Reactions)

PRECAUTIONS

Drug Interactions (See Clinical Pharmacology)

DIFLUCAN (fluconazole) increased the prothrombin time after warfarin administration Careful monitoring of prothrombin time in patients receiving DIFLUCAN and coumarin-type anticoagulants is recommended

DIFLUCAN increased the plasma concentrations of phenytoin Careful monitoring of phenytoin concentrations in patients receiving DIFLUCAN and phenytoin is recommended

DIFLUCAN has been infrequently associated with an increase in cyclosporine concentrations in renal transplant patients with or without impaired renal function Careful monitoring of cyclosporine concentrations in patients receiving DIFLUCAN and cyclosporine is recommended

DIFLUCAN increased the plasma concentrations and reduced the metabolism of tolbutamide, glyburide and glipizide When DIFLUCAN is used concomitantly with these or other sulfonylurea oral hypoglycemic agents, blood glucose concentrations should be carefully monitored, and the dose of the sulfonylurea should be adjusted as necessary

Rifampin enhances the metabolism of concurrently administered DIFLUCAN Depending on clinical circumstances, consideration should be given to increasing the dose of DIFLUCAN when it is administered with rifampin

Physicians should be aware that drug-drug interaction studies with other medications have not been conducted, but such interactions may occur

Carcinogenesis, Mutagenesis and Impairment of Fertility

Fluconazole showed no evidence of carcinogenic potential in mice and rats treated orally for 24 months at doses of 2 5, 5 or 10 mg/kg/day (approximately 2-7x the recommended human dose) Male rats treated with 5 and 10 mg/kg/day had an increased incidence of hepatocellular adenomas

Fluconazole, with or without metabolic activation, was negative in tests for mutagenicity in 4 strains of *S typhimurium*, and in the mouse lymphoma L5178Y system Cytogenetic studies *in vivo* (murine bone marrow cells, following oral administration of fluconazole) and *in vitro* (human lymphocytes exposed to fluconazole at 1000 μg/mL) showed no evidence of chromosomal mutations

Fluconazole did not affect the fertility of male or female rats treated orally with daily doses of 5 10 or 20 mg/kg or with parenteral doses of 5, 25 or 75 mg/kg, although the onset of parturition was slightly delayed at 20 mg/kg p o In an intravenous perinatal study in rats at 5, 20 and 40 mg/kg, dystocia and prolongation of parturition were observed in a few dams at 20 mg/kg (approximately 5-15x the recommended human dose) and 40 mg/kg, but not at 5 mg/kg The disturbances in parturition were reflected by a slight increase in the number of stillborn pups and decrease of neonatal survival at these dose levels The effects on parturition in rats are consistent with the species specific estrogen-lowering property produced by high doses of fluconazole Such a hormone change has not been observed in women treated with fluconazole (See Clinical Pharmacology)

Pregnancy

Teratogenic Effects. Pregnancy Category C: Fluconazole was administered orally to pregnant rabbits during organogenesis in two studies, at 5, 10 and 20 mg/kg and at 5, 25, and 75 mg/kg respectively maternal weight gain was impaired at all dose levels, and abortions occurred at 75 mg/kg (approximately 20-60x the recommended human dose), no adverse fetal effects were detected In several studies in which pregnant rats were treated orally with fluconazole during organogenesis, maternal weight gain was impaired and placental weights were increased at 25 mg/kg There were no fetal effects at 5 or 10 mg/kg, increases in fetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25 and 50 mg/kg and higher doses At doses ranging from 80 mg/kg (approximately 20-60x the recommended human dose) to 320 mg/kg embryolethality in rats was increased and fetal abnormalities included wavy ribs, cleft palate and abnormal craniofacial ossification These effects are consistent with the inhibition of estrogen synthesis in rats and may be a result of known effects of lowered estrogen on pregnancy, organogenesis and parturition

There are no adequate and well controlled studies in pregnant women DIFLUCAN should be used in pregnancy only if the potential benefit justifies the possible risk to the fetus

Nursing Mothers

It is not known whether fluconazole is excreted in human milk Because many drugs are excreted in human milk caution should be exercised when DIFLUCAN is administered to a nursing woman

Pediatric Use

Efficacy of DIFLUCAN has not been established in children A small number of patients from age 3 to 13 years have been treated safely with DIFLUCAN using doses of 3-6 mg/kg daily

ADVERSE REACTIONS

Sixteen percent of over 4000 patients treated with DIFLUCAN (fluconazole) in clinical trials of 7 days or more experienced adverse events Treatment was discontinued in 1 5% of patients due to adverse clinical events and in 1 3% of patients due to laboratory test abnormalities

In combined clinical trials and foreign marketing experience prior to U S marketing, patients with serious underlying disease (predominantly AIDS or malignancy) rarely have developed serious hepatic reactions or exfoliative skin disorders during treatment with DIFLUCAN (See Warnings) Two of these hepatic reactions and one exfoliative skin disorder (Stevens-Johnson syndrome) were associated with a fatal outcome Because most of these patients were receiving multiple concomitant medications, including many known to be hepatotoxic or associated with exfoliative skin disorders, the causal association of these reactions with DIFLUCAN therapy is uncertain

Clinical adverse events were reported more frequently in HIV infected patients (21%) than in non-HIV infected patients (13%), however, the patterns in HIV infected and non-HIV infected patients were similar The proportions of patients discontinuing therapy due to clinical adverse events were similar in the two groups (1 5%)

The following treatment-related clinical adverse events occurred at an incidence of 1% or greater in 4048 patients receiving DIFLUCAN for 7 or more days in clinical trials nausea 3 7%, headache 1 9%, skin rash 1 8% vomiting 1 7%, abdominal pain 1 7%, and diarrhea 1 5%

In two comparative trials evaluating the efficacy of DIFLUCAN for the suppression of relapse of cryptococcal meningitis, a statistically significant increase was observed in median AST (SGOT) levels from a baseline value of 30 IU/L to 41 IU/L in one trial and 34 IU/L to 66 IU/L in the other The overall rate of serum transaminase elevations of more than 8 times the upper limit of normal was approximately 1% in fluconazole-treated patients in clinical trials These elevations occurred in patients with severe underlying disease, predominantly AIDS or malignancies, most of whom were receiving multiple concomitant medications, including many known to be hepatotoxic The incidence of abnormally elevated serum transaminases was greater in patients taking DIFLUCAN concomitantly with one or more of the following medications rifampin, phenytoin, isoniazid, valproic acid, or oral sulfonylurea hypoglycemic agents

65-4526-00-0

Issued Jan 1990

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In Memoriam

Arizona Medical Association

Jourdonais, Leonard F., Sun City. Died Feb 5, 1990, aged 87. Graduate of Northwestern University Medical School, Chicago, 1933. Licensed in Arizona in 1940. Dr Jourdonais was a member of the Maricopa County Medical Society.

Serbin, George, Phoenix. Died Mar 23, 1990, aged 53. Graduate of University of California, Irvine, College of Medicine, 1965. Licensed in Arizona in 1969. Dr Serbin was a member of the Maricopa County Medical Society.

Skinner, Scott W., Litchfield Park. Died Jun 2, 1990, aged 66. Graduate of Hahnemann Medical College, Philadelphia, 1949. Licensed in Arizona in 1971. Dr Skinner was a member of the Maricopa County Medical Society.

California Medical Association

Argano, Beatrice J., Newport Beach. Died May 1990, aged 56. Graduate of Milan University. Licensed in California in 1977. Dr Argano was a member of the Orange County Medical Association.

Atteberry, Clarence V., Biggs. Died Apr 18, 1990, aged 91. Graduate of Loma Linda University, Loma Linda, California, 1927. Dr Atteberry was a member of the Humboldt-Del Norte Medical Society.

Black, Daniel W., Oakland. Died May 11, 1990, aged 66. Graduate of University of Pittsburgh School of Medicine, 1946. Licensed in California in 1946. Dr Black was a member of the Alameda-Contra Costa Medical Association.

Boylan, Richard N., Riverside. Died Apr 11, 1990, aged 75. Graduate of Northwestern University School of Medicine, Chicago, 1939. Licensed in California in 1940. Dr Boylan was a member of the Riverside County Medical Association.

Burton, William T., Tulare. Died May 8, 1990, aged 84. Graduate of University of Illinois, Chicago, 1931. Licensed in California in 1931. Dr Burton was a member of the Tulare County Medical Society.

Carman, Charles, San Francisco. Died Apr 18, 1990, aged 70. Graduate of University of California, San Francisco, School of Medicine, 1951. Licensed in California in 1951. Dr Carman was a member of the San Francisco Medical Society.

Carpy, Mathilde P., St Helena. Died Mar 17, 1990, aged 66. Graduate of Creighton School of Medicine, Omaha, 1951. Licensed in California in 1953. Dr Carpy was a member of the Napa County Medical Society.

Carter, Norman K., Palm Desert. Died Mar 10, 1990, aged 80. Graduate of University of Southern California, 1942. Licensed in California in 1942. Dr Carter was a member of the Orange County Medical Association.

Clark, Ralph D., San Francisco. Died Mar 1, 1990, aged 52. Graduate of Emory University, Atlanta, 1964. Licensed in California in 1973. Dr Clark was a member of the San Francisco Medical Society.

Cosentino, Joseph P., Sacramento. Died Apr 12, 1990, aged 72. Graduate of College of Osteopathic Physicians, 1944, and University of California, Irvine, College of Medicine, 1962. Licensed in California in 1946. Dr Cosentino was a member of the Sacramento-El Dorado Medical Society.

Davis, Fenimore E., Livermore. Died May 3, 1990, aged 84. Graduate of University of Michigan Medical School, Ann Arbor, 1935. Licensed in California in 1945. Dr Davis was a member of the Alameda-Contra Costa Medical Association.

Dougan, C. Alvin, Napa. Died Mar 16, 1990, aged 89. Graduate of Loma Linda University School of Medicine, Loma Linda, California, 1931. Licensed in California in 1948. Dr Dougan was a member of the Napa County Medical Society.

Elerding, Charles E., Garden Grove. Died May 1990, aged 60. Graduate of University of Southern California, 1956. Licensed in California in 1957. Dr Elerding was a member of the Orange County Medical Association.

Elliott, Arthur C., Santa Ana. Died Feb 11, 1990, aged 88. Graduate of University of Kansas, Kansas City, 1936. Licensed in California in 1938. Dr Elliott was a member of the Orange County Medical Association.

Flood, William R., Concord. Died Apr 4, 1990, aged 72. Graduate of University of Oklahoma College of Medicine, Oklahoma City, 1941. Licensed in California in 1947. Dr Flood was a member of the Alameda-Contra Costa Medical Association.

Freed, James Francis, San Bernardino. Died Jan 15, 1990, aged 42. Graduate of University of California, Irvine, College of Medicine, 1974. Licensed in California in 1957. Dr Freed was a member of the San Bernardino County Medical Society.

Frey, Norbert B., Sacramento. Died Apr 29, 1990, aged 80. Graduate of University of Minnesota Medical School, Minneapolis, 1936. Licensed in California in 1940. Dr Frey was a member of the Sacramento-El Dorado Medical Society.

Goodman, Leo M., Fresno. Died May 30, 1990, aged 79. Graduate of Jefferson Medical College, Philadelphia. Licensed in California in 1941. Dr Goodman was a member of the Fresno-Madera Medical Society.

Gullock, Alvin H., Dixon. Died Mar 18, 1990, aged 66. Graduate of University of California, San Francisco, 1958. Licensed in California in 1959. Dr Gullock was a member of the Solano County Medical Society.

Higgins, Joseph P., Oxnard. Died Mar 15, 1990, aged 77. Graduate of Creighton School of Medicine, Omaha. Licensed in California in 1942. Dr Higgins was a member of the Ventura County Medical Society.

Hogue, William J., Huntington Park. Died May 8, 1990, aged 89. Graduate of Rush Medical School, Chicago. Licensed in California in 1927. Dr Hogue was a member of the Los Angeles County Medical Association.

(Continued on page 250)

In Memoriam

(Continued from page 249)

Hsu, Chi Pen, Fresno. Died Feb 3, 1990, aged 56. Graduate of National Defense Medical Center, Taiwan, 1965. Licensed in California in 1980. Dr Hsu was a member of the Fresno-Madera Medical Society.

Huffer, John C., Castro Valley. Died May 11, 1990, aged 60. Graduate of University of Chicago, 1952. Licensed in California in 1956. Dr Huffer was a member of the Alameda-Contra Costa Medical Association.

McDougal, Jack E., San Luis Obispo. Died Apr 27, 1990, aged 62. Graduate of Northwestern University Medical School, Chicago, 1959. Licensed in California in 1962. Dr McDougal was a member of the San Luis Obispo County Medical Society.

Mendelsohn, Paul A., Napa. Died Apr 15, 1990, aged 32. Graduate of University of Southern California School of Medicine, Los Angeles, 1987. Dr Mendelsohn was a member of the Napa County Medical Society.

Miles, Robert H., Alameda. Died Mar 1, 1990, aged 87. Graduate of University of Oregon Medical School, Portland, 1929. Licensed in California in 1929. Dr Miles was a member of the Alameda-Contra Costa Medical Association.

Olsen, Elwood, San Francisco. Died May 8, 1990, aged 96. Graduate of University of California, San Francisco, School of Medicine, 1922. Licensed in California in 1923. Dr Olsen was a member of the San Francisco Medical Society.

Otto, Evan, La Jolla. Died May 1990, aged 63. Graduate of Northwestern University, Chicago. Licensed in California in 1957. Dr Otto was a member of the San Diego County Medical Society.

Piper, Donald F., Sacramento. Died Mar 25, 1990, aged 52. Graduate of Baylor College of Medicine, Houston, 1965. Licensed in California in 1965. Dr Piper was a member of the Sacramento-El Dorado Medical Society.

Poenisch, Paul, San Francisco. Died Mar 31, 1990, aged 59. Graduate of University of Wisconsin, Madison, 1957. Licensed in California in 1964. Dr Poenisch was a member of the San Francisco Medical Society.

Powell, Parker M., Fresno. Died May 19, 1990, aged 56. Graduate of University of California, San Francisco, School of Medicine, 1958. Licensed in California in 1959. Dr Powell was a member of the Fresno-Madera Medical Society.

Ryan, Philip B., Sacramento. Died Apr 29, 1990, aged 76. Graduate of University of Bristol, England, 1937. Licensed in California in 1961. Dr Ryan was a member of the Sacramento-El Dorado Medical Society.

Saifer, Phyllis L., Berkeley. Died Mar 26, 1990, aged 49. Graduate of University of California, San Francisco, 1966. Licensed in California in 1967. Dr Saifer was a member of the Alameda-Contra Costa Medical Association.

Shore, Fred A., Ventura. Died Mar 1990, aged 89. Graduate of Rush Medical College, Chicago, 1928. Dr Shore was a member of the Ventura County Medical Society.

Stegman, Samuel, San Francisco. Died Mar 15, 1990, aged 51. Graduate of Indiana University, Indianapolis, 1965. Licensed in California in 1973. Dr Stegman was a member of the San Francisco Medical Society.

Swerdlow, Ralph H., Sacramento. Died Apr 17, 1990, aged 63. Graduate of University of Illinois, Chicago, 1949. Licensed in California in 1962. Dr Swerdlow was a member of the Sacramento-El Dorado Medical Society.

Trujillo, Michael C., Redwood City. Died May 2, 1990, aged 43. Graduate of Stanford University, Stanford, California, 1975. Licensed in California in 1977. Dr Trujillo was a member of the San Mateo County Medical Society.

Vanbruggen, Robert E., Campbell. Died May 31, 1990, aged 71. Graduate of University of Oregon, Portland, 1955. Licensed in California in 1956. Dr Vanbruggen was a member of the Santa Clara County Medical Association.

Wood, Newell E., San Jose. Died Apr 12, 1990, aged 68. Graduate of University of Minnesota Medical School, 1945. Licensed in California in 1952. Dr Wood was a member of the Santa Clara County Medical Association.

Denver Medical Society

Abrums, William W. Died Jun 13, 1990, aged 74. Graduate of University of Colorado School of Medicine, Denver, 1940. Licensed in Colorado in 1940.

Anderl, Vernon K. Died Jul 25, 1990, aged 77. Graduate of University of Nebraska College of Medicine, Omaha, 1941. Licensed in Colorado in 1950.

Hepner, Harold Joseph. Died Jun 26, 1990, aged 67. Graduate of University of Colorado School of Medicine, Denver, 1952. Licensed in Colorado in 1953.

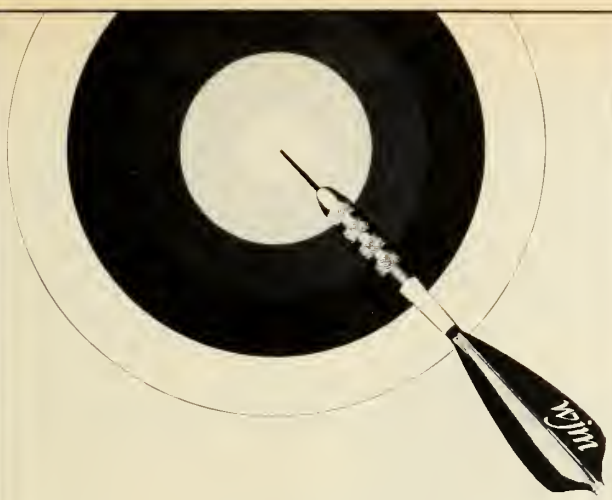
New Mexico Medical Society

Burstein, Rochelle, Albuquerque. Died Mar 23, 1990, aged 47. Graduate of Albert Einstein College of Medicine, Bronx, NY, 1968. Licensed in New Mexico in 1976. Dr Burstein was a member of the Greater Albuquerque Medical Association.

Utah Medical Association

Fish, Murland W., Salt Lake City. Died Jan 17, 1990, aged 89. Graduate of Northwestern University Medical School, Chicago. Licensed in Utah in 1932. Dr Fish was a member of the Salt Lake County Medical Society and Utah County Medical Society.

Lee, Tunnie F., Salt Lake City. Died Feb 25, 1990, aged 82. Graduate of University of Oregon, Portland, 1937. Licensed in Utah in 1939. Dr Lee was a member of the Salt Lake County Medical Society.



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Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalmic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon® is indicated as a sympathicolytic and mydriatric. It may have activity as an aphrodisiac.

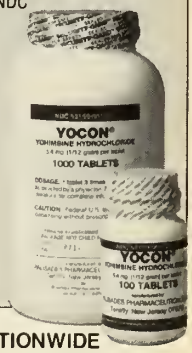
Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.[1,2] Also dizziness, headache, skin flushing reported when used orally.[1,3]

Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.[1,3,4] 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to ½ tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.[3]

How Supplied: Oral tablets of Yocon® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.



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1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

October 5-6—**Cancer Reviews.** Mayo Clinic-Scottsdale at Orange Tree Golf and Conference Center, Scottsdale. Fri-Sat. Contact: Jodi Lee Smith, (602) 391-8300.

October 12-14—**Advances in Drug Therapy.** American College of Clinical Pharmacology and University of Arizona College of Medicine at the Arizona Inn, Tucson. Fri-Sun. Contact: Lynne Mascarella, (602) 626-7832.

October 19-20—**Common Clinical Problems in the Elderly and Nursing Home Care.** Arizona Geriatrics Society at Arizona Golf Resort and Conference Center, Mesa. Fri-Sat. Contact: Marian Richardson, (602) 974-4212.

October 25—**Pediatric Emergencies: A Practical Approach.** University of Arizona at Hotel Park Tucson, Tucson. Contact: Lynne Mascarella, (602) 626-7832.

November 8-10—**Third Annual Spine Workshop.** Barrow Neurological Institute at Marriott's Mountain Shadows Resort, Scottsdale. Thurs-Sat. Contact: Toby Jardine, RN, MA, (602) 285-3178 or 1-800-Barrow-1.

November 15-18—**Psychiatric Medicine in the '90s: The Emergence of Consultation/Liaison Psychiatry.** Academy of Psychosomatic Medicine, 37th Annual Meeting, at The Pointe—Squaw Peak, Phoenix. Thurs-Sun. Contact: (312) 784-2025.

November 16-17—**Techniques in Gynecologic Surgery.** Mayo Clinic-Scottsdale at Hyatt Regency Scottsdale at Gainey Ranch, Scottsdale. Fri-Sat. Contact: Jodi Lee Smith, (602) 391-7072.

November 18-21—**7th Annual State of the Art in Total Joint Replacement.** Harrington Arthritis Reseach Center at Scottsdale Princess Resort, Scottsdale. Sun-Wed. Contact: Nancy Neroni, (602) 254-0377.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Jodi Lee Smith, Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 391-8300.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6707.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 541-0900. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ALLERGY

September 15—**Diagnostic and Therapeutic Choices in Allergy and Immunology.** Los Angeles Society of Allergy and Clinical Immunology at Regent Beverly Wilshire Hotel, Beverly Hills. Sat. 8 hrs. Contact: Sherri Cartwright, 1626 N Wilcox, No 557, Hollywood 90028. (818) 240-6735.

September 22—**Allergy and the Environment.** Allergy Foundation of Northern California at Portman Hotel, San Francisco. Sat. 7 hrs. Contact: Theodore Chu, MD, (408) 243-2700.

ANESTHESIOLOGY

October 28-November 2—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Westin Maui Hotel, Kaanapali Beach, Hawaii. Sun-Fri. 20 hrs. $345. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

November 16-18—**Anesthesiology Update: 1990.** UCD at Monterey Plaza. Fri-Sun. 14 hrs. $350. Contact: UCD.

January 20-26—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Sheraton Hotel, Poipu Beach, Kauai. Sun-Sat. 20 hrs. $345. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

January 25-27—**29th Clinical Conference in Pediatric Anesthesiology.** Children's Hospital Pediatric Anesthesiology Foundation at Stouffer Concourse Hotel. Fri-Sun. 15 hrs. Contact: Katherine Barky, MD, PO Box 54700, Los Angeles 90054.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Avenue, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7186.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

(Continued on Page 256)

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(Continued from Page 252)

February 3-8—**Clinical Update in Anesthesiology.** Biennial Western Conference on Anesthesiology at Stouffer's Wailea Beach Resort, Maui, Hawaii. Sun-Fri. Contact: Murray Atnikov, MD, c/o PO Box F110-63, Blaine, WA 98230. (604) 874-5291.

CARDIOLOGY

September 14-15—**Series I—Coronary Heart Disease Update.** Medical Education Resources at Las Vegas Hilton. Fri-Sat. 11 hrs. $295. Contact: MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80123. (800) 421-3756.

October 12-14—**Coronary Interventions: 1990.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Fri-Sun. 17 hrs. $550. Contact: Susan Buntjer, 400S, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

October 13—**Myocardial Infarction: Contemporary Management.** UCD at Hyatt Regency, Sacramento. Sat. Contact: UCD.

October 19-20—**Series I—Coronary Heart Disease Update.** Medical Education Resources at Grand Hyatt Union Square, San Francisco. Fri-Sat. 11 hrs. $295. Contact: MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80123. (800) 421-3756.

October 26-27—**Series II—Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Las Vegas Hilton. Fri-Sat. 12 hrs. $275. Contact: MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80123. (800) 421-3756.

December 1—**8th Annual Reider Laser Center: International Pulmonary Symposium on Brachytherapy and Argon and ND: YAG Lasers with ND: YAG Laser Workshop.** Memorial/UCI Center for Health Education at Long Beach. Sat. Contact: UCI.

January 24-26—**Cardiology '91.** Cardiovascular Institute at La Jolla Marriott. Thurs-Sat. Contact: Janice Turner, PO Box 2586, La Jolla 92038. (619) 459-1564.

DERMATOLOGY

October 20-21—**The Skin from A to Z.** UCSF at Laurel Heights Campus, San Francisco. Sat-Sun. 10 hrs. $205. Contact: UCSF.

January 17-19—**Workshop in Dermatopathology.** Scripps Clinic and Research Foundation at Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Sat. 20 hrs. $400. Contact: Susan J Buntjer, 400S, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

January 24-26—**Cutaneous Malignancies: 1991 Skin Cancer Update.** Scripps Clinic and Research Foundation at Hyatt Regency, La Jolla. Thurs-Sat. 12 hrs. $350. Contact: Susan Buntjer, 400S, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

EMERGENCY MEDICINE

October 11-13—**Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Hyatt Union Square. Thurs-Sat. 15 hrs. $375. Contact: UCSF.

October 22-26—**Postgraduate Institute for Primary Care and Emergency Physicians Symposium I: Cardiology, Pulmonary, Neurology.** Mon-Fri. 32 hrs. $450. Contact: UCSD.

October 29-November 3—**Topics in Emergency Medicine.** UCSF at Holiday Inn Golden Gate. Mon-Sat. 32 hrs. $460. Contact: UCSF.

November 12-16—**Emergency Medicine Symposium III: Pediatrics, OB/GYN, Legal Aspects, Dermatology.** UCSD at Hyatt Regency, La Jolla. Mon-Fri. 32 hrs. $450. Contact: UCSD.

December 10-14—**Emergency Medicine Symposium II: Trauma and Surgery.** UCSD at La Jolla Marriott. Mon-Fri. 32 hrs. $485. Contact: UCSD.

January 14-18—**Emergency Medicine Symposium I: Cardiology, Pulmonary, Neurology.** UCSD at Hyatt Regency, La Jolla. 32 hrs. $485. Contact: UCSD.

FAMILY PRACTICE/PRIMARY CARE

October 3-5—**Primary Care Medicine: Principles and Practice.** UCSF at Holiday Inn Golden Gateway, San Francisco. Wed-Fri. 19 hrs. $425. Contact: UCSF.

November 10-11—**Desert Medical Series II: Family Crisis in Family Medicine—Dealing with the Dilemmas of Aging.** Annenberg Center for Health Sciences at Eisenhower. Sat-Sun. Contact: ACHS, 39000 Bob Hope Dr, Rancho Mirage 92270. (800) 321-3690.

January 31-February 2—**Adolescent Medicine for the Practitioner.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Sat. Contact: Laurie Jones, Box 400S, Scripps Clinic, 10666 N Torrey Pines Road, La Jolla 92037. (619) 554-9592.

February 11-15—**Family Practice Refresher Course.** UCI at Westin South Coast Plaza, Costa Mesa. Mon-Fri. Contact: UCI.

February 20-23—**The Practicing Physician's Approach to the Difficult Headache Patient.** Scripps Clinic and Research Foundation and Diamond Headache Clinic at Wyndham Hotel, Palm Springs. Wed-Sat. 15 hrs. Contact: Idell Applebaum, 5252 N Western Ave, Chicago, IL 60625. (312) 878-5558.

INTERNAL MEDICINE

September 14-16—**Gastroenterology.** UCSF at San Francisco Hilton and Towers. Fri-Sun. 17 hrs. $415. Contact: UCSF.

September 22—**Growth Factors in Clinical Medicine.** Scripps Clinic and Research Foundation. Sat. 4 hrs. $75. Contact: Susan Buntjer, 400S, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

October 18-20—**Breast Cancer Seminar.** Memorial/UCI Center for Health Education at Stouffer Hotel, Palm Springs. Thurs-Sat. Contact: UCI.

October 22-24—**14th Annual Cancer Symposium.** Scripps Memorial Hospital at Sheraton Harbor Island Hotel, San Diego. Mon-Wed. 20 hrs. $390. Contact: Meeting Management, 5665 Oberlin Dr, Ste 110, San Diego 92121. (619) 453-6222.

October 20—**Lipids Conference.** UCD at Sheraton Sunrise, Sacramento. Sat. Contact: UCD.

November 9-10—**Metabolic Control of Diabetes.** Memorial/UCI Center for Health Education at Westin South Coast Plaza, Costa Mesa. Fri-Sat. Contact: UCI.

November 30-December 1—**Northern California Internal Medicine Update.** UCD at Hilton Inn. Fri-Sat. Contact: UCD.

December 6-9—**Fall Symposium on Back Pain.** American Back Society at San Francisco Marriott Hotel. Thurs-Sun. 18 hrs. Contact: Aubrey Swartz, MD, ABS, 2647 E 14th St, Ste 401, Oakland 94601. (415) 536-9929.

January 31-February 2—**Advanced Nephrology: Nephrology for the Consultant.** UCSD at Sheraton Grand Hotel, San Diego. Thurs-Sat. 17 hrs. $350. Contact: Meeting Management, 5665 Oberlin Dr, Ste 110, San Diego 92121. (619) 453-6222.

February 1-3—**8th Annual Reider Laser Symposium-Urology.** Memorial/UCI Center for Health Education at Palm Springs. Fri-Sun. Contact: UCI.

February 15-17—**24th Annual Recent Advances in Neurology.** UCSF at San Francisco. Fri-Sun. 15 hrs. Contact: UCSF.

February 18-20—**Clinical Hematology and Oncology: 1991.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Wed. 18 hrs. $385. Contact: Susan Buntjer, 400S, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

OB/GYN

November 8-11—**Current Issues in Perinatal Medicine.** Memorial/UCI Center for Health Education at Marriott's Rancho Las Palmas Resort, Palm Springs. Thurs-Sun. Contact: UCI.

November 11-17—**13th Annual Review Course in Clinical OB/GYN and/or Gynecological Histopathology.** Memorial/UCI Center for Health Education at Westin South Coast Plaza, Costa Mesa. 1 week. Contact: UCI.

November 29-December 1—**Nebraska OB/GYN Society Meeting.** Nebraska OB/GYN at Las Vegas, Nevada. Thurs-Sat. Contact: University of Nebraska Medical Center, 42nd and Dewey Ave, Omaha, NE 68105-1065. (402) 559-4152.

February 1-3—**8th Annual Reider Laser Symposium-Gynecology.** Memorial/UCI Center for Health Education at Palm Springs. Fri-Sun. Contact: UCI.

February 14-17—**46th Annual Postgraduate Assembly.** OB-GYN Assembly of Southern California at Beverly Hilton Hotel, Beverly Hills. Thurs-Sun. 28 hrs. Contact: OB-GYN Assembly, 5820 Wilshire Blvd, No. 500, Los Angeles 90036. (213) 937-5514.

(Continued on Page 258)

What we've done for you lately.

We've taken some concrete steps toward making the less exciting parts of your job less of a problem.

Here's what we did.

We developed ways to speed up claims processing and payments. So you can spend more time worrying about patients, and less time worrying about paperwork.

Our new One Call system helps speed up utilization review and preauthorization. So you can get immediate answers to your benefit and eligibility questions with just one call.

And without being transferred or put on hold.

We've also developed a program called Claim Free™, which further expedites the reimbursement process by eliminating paper claims for both you and your Medicare subscribers.

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And, by taking better care of you, we're doing just that.

Blue Cross of California

We care about what's good for you.

(Continued from Page 256)

OCCUPATIONAL AND ENVIRONMENTAL MEDICINE

October 2-7—**Sports Medicine Update.** Memorial/UCI Center for Health Education at Mauna Kea Hotel, Hawaii. Tues-Sun. Contact: UCI.

October 8-19—**Occupational and Environmental Medicine Session II.** UCSF at Cathedral Hill Hotel, San Francisco. 1½ weeks. 80 hrs. $1,200. Contact: UCSF.

October 15-19—**Current Topics in Occupational Medicine.** UCSF at Cathedral Hill Hotel, San Francisco. Mon-Fri. 40 hrs. $600. Contact: UCSF.

OPHTHALMOLOGY

September 17-18—**Blepharoplasty Workshop: Principles and Technique.** UCSF at Portman and Chancellor Hotels, San Francisco. Mon-Tues. 11 hrs. $690. Contact: UCSF.

September 21-22—**Corneal & Refractive Surgery for the Anterior Segment Surgeon: A Symposium Commemorating Max Fine, MD.** Pacific Presbyterian Medical Center at Fairmont Hotel, Nob Hill, San Francisco. Sat-Sun. 10 hrs. $350. Contact: Pacific Vision Foundation, PPMC, (415) 923-3423.

November 30-December 2—**American Academy of Ophthalmology Regional Update Course.** American Academy of Ophthalmology at Los Angeles. Fri-Sun. Contact: Gary Holland, (213) 825-9508.

December 13-14—**New Ideas on Common Retinal Disorders.** UCSF at Grand Hyatt Union Square, San Francisco. Thurs-Fri. Contact: UCSF.

January 13-16—**Contact Lens Association of Ophthalmologists 1991 Annual Meeting.** CLAO at Caesars Palace, Las Vegas, Nevada. Sun-Wed. Contact: CLAO, 523 Decatur St, Ste One, New Orleans, LA 70130-1027. (504) 581-4000.

February 8-10—**60th Midwinter Clinical Conference.** Research Study Club of Los Angeles at Moseley/Salvatori Conference Center, Los Angeles. Fri-Sun. Contact: Research Study Club, PO Box 1216, Murrieta 92362. (714) 677-4482.

ORTHOPEDICS

October 4-6—**Orthopedic Update.** UCSD at Hyatt La Jolla. Thurs-Sat. Contact: Pat Curl, PO Box 33185, San Diego 92103. (619) 692-9115.

December 6—**Common Musculosketal Problems—Foot and Ankle.** VA Medical Center Sepulveda. Thurs. 5 hrs. Contact: Arun Mehta, MD, Rehabilitation Medicine Service (117), VAMC Sepulveda 91343. (818) 895-9344.

OTOLARYNGOLOGY

November 8-10—**Otolaryngology Update: 1990.** UCSF at Union Square Holiday Inn, San Francisco. Thurs-Sat. 18 hrs. $375. Contact: UCSF.

February 8-10—**60th Midwinter Clinical Conference.** Research Study Club of Los Angeles at Moseley/Salvatori Conference Center. Fri-Sun. Contact: Research Study Club, PO Box 1216, Murrieta 92362. (714) 677-4482.

PATHOLOGY

October 4-6—**International Symposium on Medical Virology.** UCI at Four Seasons Hotel, Newport Beach. Thurs-Sat. Contact: Luis M. de la Maza, (714) 634-6868.

October 12-13—**Advances in Rheumatology and Progress Against Infectious Diseases: 5th Annual Kuzell Institute Symposia.** Pacific Presbyterian Medical Center at Le Meridien Hotel, Grand Ballroom, San Francisco. Fri-Sat. 12 hrs. $60. Contact: CME Dept. PPMC, (415) 923-3441.

October 12-14—**8th Postgraduate Course in Medical Mycology (Dermatomycology).** UCSF. Fri-Sun. 16 hrs. $295. Contact: UCSF.

October 19—**Fine Needle Aspiration Tutorials.** UCSF. Fri. 7 hrs. Contact: UCSF.

October 20—**30th Annual Scientific Symposium on Kidney Disease.** National Kidney Foundation of Southern California at Wyndham Palm Springs. Sat. Contact: Sylvie Tarro, 5777 W Century Blvd, Ste 395, Los Angeles 90045. (213) 641-8152.

November 2-3—**Update on Thyroid Disease—1990.** UCSF at Hyatt Regency Embarcadero, San Francisco. Fri-Sat. 12 hrs. $150. Contact: UCSF.

November 10—**Infectious Diseases in Critical Care.** UCD at Hilton Inn, Sacramento. Sat. Contact: UCD.

February 13-15—**Clinical Laboratory Molecular Analysis.** Scripps Clinic and Research Foundation at Hyatt Regency Hotel, La Jolla. Wed-Fri. 21 hrs. $375. Contact: Laurie Jones, Box 400S, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-9592.

PEDIATRICS

October 7-14—**15th Annual Pediatrics for the Practitioner.** Memorial/UCI Center for Health Education at Mauna Kea Hotel, Hawaii. 1 week. Contact: UCI.

October 18-21—**47th Annual Brennemann Memorial Lectures.** Los Angeles Pediatric Society at San Diego Marriott-La Jolla Hotel, La Jolla. Thurs-Sun. 15 hrs. $325. Contact: LAPS, (213) 757-1198.

November 9-11—**Infectious Diseases in Children.** Children's Hospital Oakland at Monterey Plaza Hotel on Cannery Row. Fri-Sun. 12 hrs. $280. Contact: Kim Leadon, 747 52nd St, Oakland 94609. (415) 428-3021.

December 1—**8th Annual Binational Pediatric Conference.** Children's Hospital San Diego at Mercy Hospital Education Center, San Diego. Sat. 5 hrs. Contact: CME Dept, Children's Hospital, (619) 576-4072.

December 8-9-**Stabilization and Management of the Critically Ill Child.** UCSF at Hyatt Regency Hotel, San Francisco. Sat-Sun. 9 hrs. Contact: UCSF.

January 23-26—**Health Science Response to Child Maltreatment 1991.** Children's Hospital San Diego at U S Grant Hotel, San Diego. Wed-Sat. 22 hrs. Contact: Children's Hospital, (619) 576-5814.

February 8-10—**Current Concepts in Pediatric Medicine 1991.** Children's Hospital San Diego at Hyatt Islandia Hotel, San Diego. Fri-Sun. 18 hrs. Contact: CME Dept. Children's Hospital, (619) 576-4072.

PSYCHIATRY

September 22—**Alcohol/Drug Dependency: A Medical Challenge—The Physician's Role in Treatment.** UCLA at Neuropsychiatric Institute Auditorium, Los Angeles. Sat. 5 hrs. $70. Contact: UCLA.

October 11-12-**No Crystal Stair: Models for Successful Development of Afro-Americans.** UCSF at Laurel Heights Campus, San Francisco. Thurs-Fri. Contact: UCSF.

October 19-21—**Creating an Integrated Psychiatry: Challenge of the 90's.** California Psychiatric Association at Claremont Hotel, Berkeley. Fri-Sun. 11 hrs. Contact: Barbara Gard, 1100 N St, Ste 2-E, Sacramento 95814. (916) 442-5196.

October 26-27—**The Aftermath of Suicide: Counseling Survivors.** UCSF on Campus. Fri-Sat. $190. Contact: UCSF.

November 9-11—**36th Annual Group Therapy Symposium.** UCSF at Sir Francis Drake Hotel, San Francisco. Fri-Sun. Contact: UCSF.

November 12-16—**Introduction to Medical Hypnosis.** UCSD at Inn at Del Mar. Mon-Fri. Contact: UCSD.

RADIOLOGY

October 6-7—**Ultrasound: 1990.** UCD at Red Lion Inn, Sacramento. Sat-Sun. 10 hrs. $195. Contact: UCD.

October 20-21—**Advanced Imaging of the Musculoskeletal System.** UCSD at Hotel del Coronado. Sat-Sun. 12 hrs. $125. Contact: UCSD.

October 22-26—**15th Annual San Diego Postgraduate Course.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 27 hrs. $300. Contact: UCSD.

October 26-28—**10th Annual Interventional Radiology.** UCSD at Hotel del Coronado, San Diego. Fri-Sun. 18 hrs. $350. Contact: UCSD.

November 9-11—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton Resort Hotel, Laguna Niguel. Fri-Sun. 20 hrs. $400. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 258)

December 7-9—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton Resort Hotel, Laguna Niguel. Fri-Sun. 18 hrs. $400. Contact: UCSD.

January 19-21—**Advanced Seminars in Diagnostic Imaging.** UCSF at Ritz-Carlton Resort Hotel, Laguna Niguel. Sat-Mon. 20 hrs. $400. Contact: UCSF.

February 1-3—**43rd Midwinter Radiological Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Fri-Sun. 17 hrs. $395. Contact: LARS, PO Box 91215, Los Angeles 90009-1215. (213) 827-9078.

February 4-5—**Angio-Interventional Radiology.** UCSD at Le Meridien Hotel, San Diego. Mon-Tues. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 5-9—**17th Annual Mid-Pacific Radiological Conference.** Los Angeles Radiological Society at Maui Marriott Hotel, Maui, Hawaii. Tues-Sat. 16 hrs. $395. Contact: LARS, PO Box 91215, Los Angeles 90009. (213) 827-9078.

February 6—**Intraluminal Ultrasound.** UCSD at Le Meridien Hotel, San Diego. Wed. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 6—**Basic Introduction to Doppler Principles.** UCSD at Le Meridien Hotel, San Diego. Wed. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 11-15—**Contemporary Diagnostic Imaging Featuring MRI, CT, US and Interventional Radiology.** Stanford University at Ritz-Carlton Hotel, Mauna Lani, Hawaii. Mon-Fri. 20 hrs. $515. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

REHABILITATIVE/THERAPEUTIC

November 9-10—**2nd Annual Symposium-Diagnosis and Treatment of Bone and Soft Tissue Tumors: A Multidisciplinary Approach.** UCD at Hyatt Regency, Sacramento. Fri-Sat. 14 hrs. $345. Contact: UCD.

January 23-26—**6th International Symposium on Platinum and Other Metal Coordination Compounds in Cancer Chemotherapy.** UCSD at Sheraton Harbor Island East Hotel, San Diego. Wed-Sat. Contact: Cass Jones, 7916 Convoy Ct, San Diego 92111. (619) 565-9921.

February 7-9—**Biotherapy of Cancer: A Symposium for Clinicians and Nurses.** Hoag Hospital at Newport Beach Marriott. Thurs-Sat. 15 hrs. $375. Contact: Nomi Feldman, 5665 Oberlin Dr, Ste 110, San Diego 92121. (619) 453-6222.

SURGERY

September 1990-December 1990—**Temporal Bone Surgical Dissection Courses: 1990.** House Ear Institute, 5 days per month. 53 hrs. $975. Contact: Antonio de la Cruz, MD, Director of Education, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

October 6-8—**Anatomic Basis for Aesthetic Surgery: Hands-On Laboratory Course.** UCD at Hyatt Regency, Davis. Sat-Mon. Contact: UCD.

November 12-16—**Hyperbaric Medicine.** UCI/Memorial Medical Center at Long Beach. Mon-Fri. 30 hrs. $650. Contact: Celia Loney, 2801 Atlantic Ave, PO Box 1428, Long Beach 90801. (213) 595-2000.

November 17—**C02 Surgical Laser Workshop.** Scripps Clinic and Research Foundation. Sat. 8 hrs. $600. Contact: Susan Buntjer, Box 400S, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

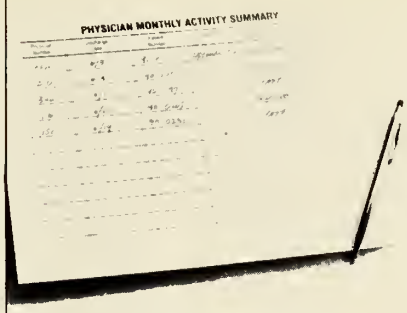
January 18-19-**What's New in General Surgery: 13th Annual Postgraduate Course.** UCD at Capitol Plaza Holiday Inn, Sacramento. Fri-Sat. Contact: UCD.

OF INTEREST TO ALL PHYSICIANS

October 10-14—**Advances in Specialty Care.** Mission Hospital Regional Medical Center. Wed-Sun. 15 hrs. $190. Contact: Jane Moore, Mission Hospital, 27700 Medical Center Rd, Mission Viejo 92691. (714) 364-7756.

October 13—**10th Annual Norman Sharrer Symposium: Drug Dependency and the Practicing Physician.** Kaweah Delta District Hospital at Lamplighter Inn Visalia. Sat. 5 hrs. $25. Contact: Brooke Mack, (209) 625-7308.

(Continued on Page 260)



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This course will familiarize the practioner with evaluating and treating transplant candidates. It will cover challenges the patients face, such as shortage of donors, immunosuppressive medications, drug interactions, rejections, infections, and cost. The course will address renal, pancreas, liver, cardiac, lung, corneal, and bone marrow transplantation.

Sponsored by the University of Washington Medical Center, School of Medicine, and Department of Surgery.

For information call the Office of Continuing Medical Education, (206) 543-1050 or (800) 869-2633.

CONTINUING MEDICAL EDUCATION

(Continued from Page 259)

November 18-21—**Putting Prevention into Practice.** SDSU at Hyatt Islandia Hotel, San Diego. Sun-Wed. 23 hrs. $140. Contact: Mickey Pagan, (619) 594-5904.

February 18-20—**11th Betty Ford Center Conference on Chemical Dependency.** Annenberg Center for Health Sciences. Mon-Wed. Contact: ACHSE, 39000 Bob Hope Dr, Rancho Mirage 92270. (800) 321-3690.

February 20-23—**The Practicing Physician's Approach to the Difficult Headache Patient.** Scripps Clinic and Diamond Headache Clinic at Wyndham Hotel, Palm Springs. Wed-Sat. 15 hrs. Contact: Idell Applebaum, 5252 N Western Ave, Chicago, IL 60625. (312) 878-5558.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

September 20—**Colorado Radiological Society.** Hyatt Regency DTC, Denver. Thurs. Contact: Carol Goddard, (303) 770-6048.

September 20—**Colorado Society of Clinical Pathologists.** Denver, location to be announced. Thurs. Contact: Carol Goddard, (303) 770-6048.

September 21—**Current Clinical Update: Emergency Medicine for the Primary Care Physician.** Saint Joseph Hospital, Denver. Fri. Contact: Kari Edwards, (303) 837-7297.

September 22-23—**ACLS Course.** Colorado Society of Anesthesiologists at St Luke's Hospital, Denver. Sat-Sun. Contact: Carol Goddard, (303) 770-6048.

October 10-11—**Physician Preceptorship Program.** The Children's Hospital, Denver. Wed-Thurs. Contact: Pat Winter, (303) 861-6668.

October 10-14—**Western Society of Allergy and Immunology—Annual Scientific Session.** Broadmoor Hotel, Colorado Springs. Wed-Sat. Contact: Becky Smith, (503) 279-8531.

October 13—**The Changing Faces of Medicine: Professional Decisions, Personal Choices.** Saint Joseph Hospital, Denver. Sat. Contact: Kari Edwards, (303) 837-7297.

October 17-19—**Care of the Sick Newborn Conference.** The Children's Hospital, Denver. Wed-Fri. Contact: Conference Dept, Children's Hospital, (303) 861-6945.

October 18—**Colorado Radiological Society.** Hyatt Regency DTC, Denver. Thurs. Contact: Carol Goddard, (303) 770-6048.

October 18—**Colorado Society of Clinical Pathologists.** Denver, location to be announced. Thurs. Contact: Carol Goddard, (303) 770-6048.

October 22-26—**Rural Perinatal Traineeship (Level 1).** The Children's Hospital, Denver. Mon-Fri. Contact: Christie Sievers, (303) 861-5413.

October 27—**Rocky Mountain Hand Surgery Society.** Denver, location to be announced. Thurs. Contact: Carol Goddard, (303) 770-6048.

November 2-3—**Fort Collins Perinatal Conference.** The Children's Hospital at the Marriott Hotel, Fort Collins. Fri-Sat. Contact: Christie Sievers, (303) 861-6413.

November 9-10—**Western Slope Conference.** The Children's Hospital at the Red Lion Inn, Durango. Fri-Sat. Contact: Christie Sievers, (303) 861-6413.

November 12-16—**Rural Perinatal Traineeship (Level II).** The Children's Hospital, Denver. Mon-Fri. Contact: Christie Sievers, (303) 861-6413.

November 15—**Colorado Radiological Society.** Hyatt Regency DTC, Denver. Thurs. Contact: Carol Goddard, (303) 770-6048.

December 3-7—**Respiratory Therapy Traineeship.** The Children's Hospital, Denver. Mon-Fri. Contact: Jeff Griebel, (303) 861-6227.

January—**Perinatal Continuing Education Program.** The Children's Hospital, Denver Community Hospital-based, 40-week, self-study program for all perinatal healthcare providers. Contact: Pat Winter, (303) 861-6668.

(Continued on Page 262)

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If you are a resident specializing in anesthesiology, general surgery, including colon/rectal, pediatric, cardio/thoracic, plastic, orthopedic, peripheral/vascular, and neurosurgery, and would like more information on the Army Reserve Specialized Training Assistance Program (STRAP), call 1-800-USA-ARMY.

ARMY RESERVE MEDICINE. BE ALL YOU CAN BE.

CONTINUING MEDICAL EDUCATION

(Continued from Page 260)

January 17—**Colorado Radiological Society.** Hyatt Regency DTC, Denver. Thurs. Contact: Carol Goddard, (303) 770-6048.

January 26-31—**Uvetitis and Pathology.** Colorado Ophthalmological Society at Westin Hotel, Vail. Sat-Thurs. Contact: Carol Goddard, (303) 770-6048.

First Wednesday of each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver, CO. (303) 270-5195.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

September 21-22—**Southwest Psychiatric Symposium on Substance Abuse.** Hyatt Regency, Albuquerque. Fri-Sat. Contact: UNM Office of Continuing Medical Education, PO Box 713, Albuquerque 87131. (505) 277-3942.

October 4-6—**Management of Radiation Accidents.** Sheraton Old Town Hotel, Albuquerque. Thurs-Sat. Contact: UNM Office of Continuing Medical Education, PO Box 713, Albuquerque 87131. (505) 277-3942.

October 11-13—**Second International Symposium on Intrapartum Biochemical Monitoring of the Fetus.** Hyatt Regency, Albuquerque. Thurs-Sat. Contact: UNM Office of Continuing Medical Education, PO Box 713, Albuquerque 87131. (505) 277-3942.

October 12-13—**John N. Wilson, MD: Lectureship in Cardiovacular Diseases.** Hyatt Regency, Albuquerque. Fri-Sat. Contact: Ann Nelson, Presbyterian Heart Institute Foundation, PO Box 26666, Albuquerque 87125. (505) 841-1225.

October 19—**The Prevention of Infectious Diseases.** Hyatt Regency Hotel, Albuquerque. Fri. Contact: Ann Winter, 601 Grand Ave, NE, Albuquerque 87102. (505) 848-8105.

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Biomedical Science

Regulation of Immunity by Anti-T-Cell Antibodies

DAVID WOFSY, MD, *San Francisco*

Presented at the Plenary Session, Western Association of Physicians, Carmel, California, February 6, 1990.

Antilymphocyte antibodies, in the form of antilymphocyte or antithymocyte sera, have long been used as immunosuppressive agents, particularly in the setting of organ transplantation. While effective, these antisera are far from ideal. They do not focus therapy on selected molecules or functionally distinct cell subsets, but rather react with a broad range of lymphocyte surface antigens. In addition, conventional antisera typically elicit a host immune response that can interfere with efficacy and that may cause toxicity. For years, these obstacles have substantially limited the value of antilymphocyte antibodies as therapeutic agents.

In recent years, the development of monoclonal antibodies (mAb) has rekindled interest in the therapeutic applications of antilymphocyte antibodies. It is now possible to produce homogeneous antibody preparations that can identify and selectively target distinct cell subsets, surface molecules, and secreted products that regulate immune function. This achievement has led to the development of several new strategies that are designed to suppress pathologic immune responses. Because of the pivotal role of T cells in the generation of immune responses, many of these strategies are focused on T-cell antigens.

Antibodies to CD3

Monoclonal anti-T-cell antibodies were first used successfully in humans to suppress renal allograft rejection. In prospective multicenter trials, a short course of mAb to the pan-T-cell antigen, CD3 (formerly designated T3), proved to be more effective than the use of high-dose corticosteroids and azathioprine in reversing the initial rejection crisis and promoting long-term graft survival in recipients of cadaveric renal allografts.[1] These early trials showed the feasibility of using anti-T-cell mAb to modulate immune function in humans, but they were complicated by several important problems that remain to be solved. First, the initiation of therapy with anti-CD3 mAb is accompanied by marked, albeit transient, systemic side effects, including fever, dyspnea, nausea, hypotension, and occasionally shock.[1] These effects may reflect the ability of anti-CD3 to activate T cells, causing the release of cytokines.[2] It may be possible to circumvent this problem by using anti-T-cell monoclonal antibodies that do not induce T-cell activation. Second, treatment with anti-CD3 mAb, like conventional antiserum, elicits an immune response in humans that precludes repeating therapy for recurrent rejection episodes.[1,3] Finally, anti-CD3 interferes with the function of all T cells, instead of focusing its effect on T-cell subsets that may be preferentially involved in recognizing and rejecting a graft. As I will describe, several alternative strategies are now being investigated in an effort to solve these problems. These strategies involve the use of monoclonal antibodies that are aimed at subsets of T cells rather than the entire T-cell population.

Antibodies to CD4

Many T-cell antigens have been considered as potential targets for immunosuppressive therapy with monoclonal antibodies (Figure 1). These include the CD4 and CD8 antigens that define the major T-cell subsets, as well as other antigens that are limited in their expression to activated T cells or to distinct families of T-cell antigen receptors. Among these, anti-CD4 mAb recently became the first to be subjected to clinical trials in humans.[4-7] These trials are based on mounting evidence from studies in animals showing that anti-CD4 mAb can suppress diverse autoimmune diseases[8-16] and can substantially prolong the survival of histoincompatible grafts.[17,18]

The most extensive examination of the effects of anti-CD4 mAb has been conducted in the NZB/NZW F_1 (B/W) mice model for systemic lupus erythematosus. An autoimmune disease spontaneously develops in these mice that closely resembles systemic lupus erythematosus in humans.[19] Female mice are more severely afflicted than male mice. They spontaneously produce numerous autoantibodies, including antibodies to double-stranded DNA, and they die young of immune-complex glomerulonephritis. Murine lupus in B/W mice can be prevented by the long-term administration of anti-CD4 mAb.[8] Moreover, even when treatment is delayed until severe lupus nephritis has developed, long-term therapy with anti-CD4 can reverse the clinical manifestations of systemic lupus and dramatically prolong life (Figure 2).[9]

The beneficial effects of anti-CD4 mAb are not limited to B/W mice. In two other murine models for systemic lupus erythematosus that are genetically unrelated to B/W mice, MRL/Mp-lpr/lpr and BXSB, the long-term administration of anti-CD4 retards autoimmunity.[10,11] Similarly, treatment with anti-CD4 suppresses the spontaneous development of autoimmune diabetes in nonobese diabetic mice.[12,13] Anti-CD4 is also effective in several experimentally induced murine autoimmune diseases.[14-16] These include experimental allergic encephalomyelitis,[14] a model for multiple sclerosis; collagen-induced arthritis,[15] a model for rheumatoid arthritis; and experimentally induced myasthenia gravis.[16] In experimental allergic encephalomyelitis, for example, a demyelinating disease of the central nervous system is induced by immunization with a spinal cord homogenate containing myelin basic protein (MBP). In control mice, immunization with MBP causes an autoimmune disease characterized clinically by rapidly progressive paralysis within two to

(Wofsy D: Regulation of immunity by anti-T-cell antibodies. West J Med 1990 Sep; 153:265-268)

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ABBREVIATIONS USED IN TEXT

IL-2 = interleukin 2
mAb = monoclonal antibodies
MHA II = class II major histocompatibility antigen
MBP = myelin basic protein

three weeks. When the mice are treated with anti-CD4 during the early stages of neurologic deterioration, however, neurologic deficits can be reversed and progressive paralysis and death can be prevented.[14]

Based on the encouraging results of anti-CD4 therapy in murine models for autoimmunity, preliminary trials have been initiated in humans with autoimmune diseases.[4-7] Hafler and co-workers gave a short course of murine anti-CD4 mAb to four patients with chronic progressive multiple sclerosis.[7] This feasibility study did not examine therapeutic efficacy, but it showed that infusions of anti-CD4 were well tolerated clinically and did not produce the acute toxic effects seen previously in patients treated with anti-CD3.[1] Although this study was not designed to assess the suppression of disease activity, the suppression of immune function was documented by in vitro measurement of mitogen-induced stimulation of immunoglobulin synthesis. Disappointingly, despite this evidence of immune suppression, an immune response to the administered mouse mAb developed in three of the four subjects. In similar studies, Herzog and associates treated seven patients with rheumatoid arthritis with daily infusions of murine anti-CD4 mAb for a week.[4-6] Clinical side effects were minimal or absent. Immune suppression was demonstrated by a reversible inhibition of delayed-type hypersensitivity and by reduced in vitro T-cell proliferation, but, in this study, too, host immunity to the administered mAb developed in most of the patients. All patients reported a reduction in disease activity, but there were no untreated control subjects against whom to judge clinical efficacy.

The therapeutic value of anti-CD4 mAb will ultimately depend largely on our ability to block host immunity to the mAb and to minimize the suppression of normal immune function. With regard to the host immune response to therapy, recent studies in mice have shown that the immune response to xenogeneic (rat) mAb to CD4 is dose-dependent: low doses elicit an immune response, but high doses do not.[20] Furthermore, a short course of high-dose therapy induces long-term tolerance to the subsequent administration of lower doses that would ordinarily elicit an immune response.[21,22] Thus, it is possible that the immune response to anti-CD4 mAb in humans can be prevented either by sustained therapy with high doses of the mAb or by inducing tolerance initially with anti-CD4. Alternate solutions will have to be sought for other monoclonal antibodies that do not block the immune response to themselves. In certain circumstances, "humanized" antibodies composed of mouse variable regions inserted into human immunoglobulin molecules have been administered to people without eliciting a host immune response.[23] Concurrent conventional immunosuppressive therapy may also be helpful, although this has not prevented the development of host immunity to anti-CD3 mAb in transplant patients.[1]

Unfortunately, the requirement for high doses of anti-CD4 to block the host immune response to therapy has adverse implications for normal immune function. High-dose therapy profoundly depletes CD4+ cells in animals, abrogates humoral immune responses, and diminishes cellular immune responses.[20,21,24-27] Although CD4+ cells gradually reappear when treatment is stopped, a substan-

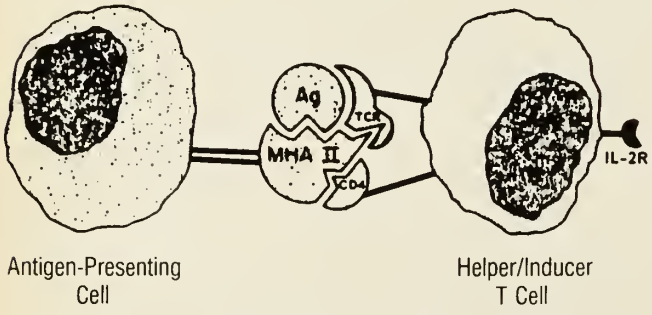

Figure 1.—Helper T cells recognize processed antigen (Ag) in association with class II major histocompatibility antigens (MHA II) on antigen-presenting cells. This recognition involves a T-cell receptor (TCR) that recognizes the Ag/MHA II complex. The interaction between T cells and antigen-presenting cells is facilitated by another T-cell surface molecule, CD4, that binds to MHA II. On exposure to Ag, activated T cells express additional surface molecules, such as the interleukin-2 receptor (IL-2R), that are not present on resting T cells. Based on this model, CD4, TCR, IL-2R, and MHA II may all be considered potential targets for immunosuppressive therapy.

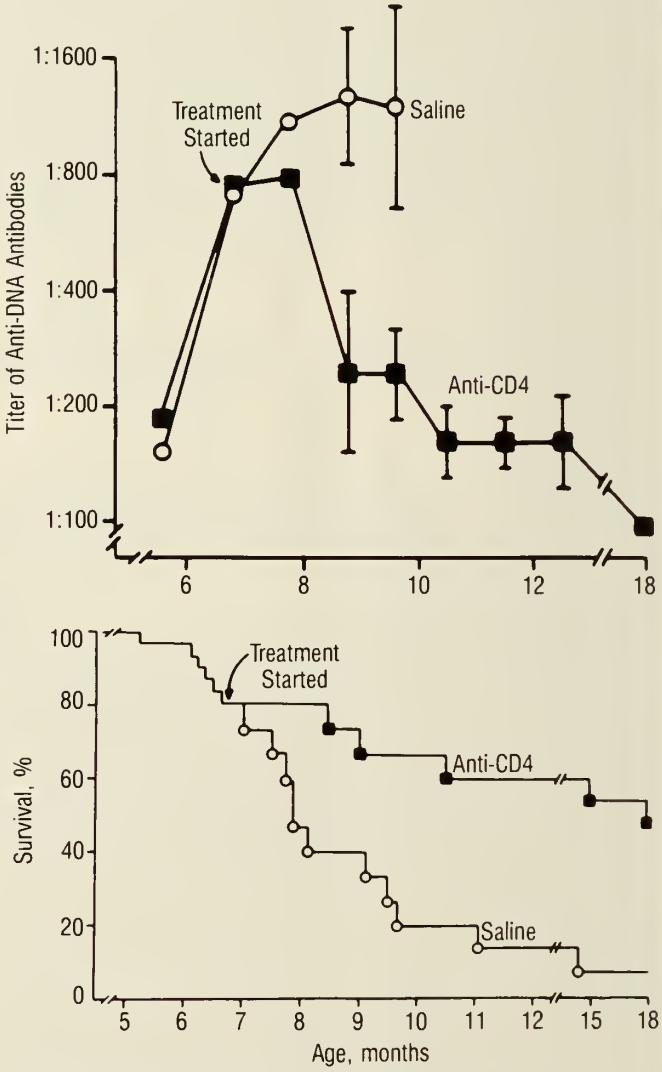

Figure 2.—Treatment with anti-CD4 retards murine lupus. Lupus-prone female NZB/NZW F_1 (B/W) mice received weekly injections of anti-CD4 (■) or saline (o) beginning at age 7 months. The top graph shows the geometric mean titer of antibodies to double-stranded DNA; the bottom indicates survival. The mice had advanced disease when treatment was initiated, as manifested by high titers of anti-DNA antibodies **(top)** and a 20% mortality rate in the original cohort **(bottom)** before therapy. Adapted from Wofsy and Seaman,[9] by copyright permission of the American Association of Immunologists.

tial depletion of target cells and the suppression of normal immune function persist for a prolonged period after the cessation of therapy.[26,27] These adverse effects can be minimized by the use of $F(ab')_2$ fragments of the mAb. The $F(ab')_2$ fragments bind CD4, inhibit target cell function, and thereby suppress autoimmunity.[22] Because the fragments lack the Fc portion of the molecule that is required for the clearance of antibody-coated cells, however, target cells are not depleted.[20,22] Consequently, the effects of the $F(ab')_2$ fragments on normal immunity are immediately reversible with the cessation of therapy (D.W., unpublished data, June 1989).

Antibodies to Activation Antigens

While it may be possible to minimize the toxicity of anti-CD4 mAb relative to high-dose corticosteroids and cytotoxic drugs, it would be far preferable to develop creative strategies to focus therapy more narrowly on the T cells that promote autoimmunity. One such strategy involves the use of mAb to antigens that are expressed on activated T cells. When T cells are activated, they express certain antigens that are not expressed on resting T cells. These activation antigens, which include the receptor for interleukin 2 (IL-2; see Figure 1), could serve as targets for specific therapy designed to interrupt active immune responses while sparing resting T cells. This hypothesis is supported by recent studies showing that mAb to the IL-2 receptor can be used in animals to suppress lupus nephritis and autoimmune diabetes.[28] Monoclonal antibodies to the IL-2 receptor have not yet been used to suppress immunity in humans, but they have been used with some success to treat humans with malignant T-cell tumors.[29] If these mAb continue to be well tolerated as chemotherapeutic agents, it is likely that they will soon be tested as immunosuppressive agents.

Antibodies to Antigen-Specific T-Cell Receptors

Ideally, therapy with anti-T-cell mAb would be directed against receptors that are expressed only by T cells that react with graft antigens (in transplant recipients) or autoantigens (in patients with autoimmune diseases). This strategy is based on the hope that alloreactive or autoreactive T cells might use a limited repertoire of T-cell receptor genes that is biased toward recognizing the disease-inducing antigens. Recent studies indicate that, at least in experimental allergic encephalomyelitis, such limited heterogeneity exists among antigen receptors on autoreactive T cells.[30] Specifically, MBP-reactive T cells use a limited subset of T-cell receptor genes; mAb directed against the products of these genes can be used to eliminate a pathologic portion of the T-cell receptor repertoire and thereby ameliorate autoimmune disease. It remains to be determined whether similar T-cell receptor targets can be identified in other clinical situations.

Antibodies to Major Histocompatibility Antigens

Many autoimmune diseases in humans are associated with particular HLA-DR antigens. These antigens, also referred to as class II major histocompatibility antigens (MHA II), play an important role in promoting immune responses. As suggested by Figure 1, the interaction between antigen-presenting cells and helper T cells can be blocked not only by mAb directed against the T-cell receptor or CD4 antigen on T cells, but also by mAb directed against MHA II on antigen-presenting cells. This suggests an appealing alternative to the use of anti-T-cell mAb to suppress autoimmunity: that is, it might be possible to retard autoimmunity by selectively interfering with the function of disease-associated MHA II. This possibility has generated great excitement recently because of the rapid progress that has been made in establishing the structure of MHA II molecules and identifying the precise sites on certain MHA II molecules that account for the predisposition to autoimmunity.[31] The enthusiasm for this approach is supported by the observation that mAb to MHA II can suppress autoimmunity in murine models for several human autoimmune diseases.[31-34] Because different MHA II molecules are co-expressed on the surface of antigen-presenting cells, the inhibition of selected MHA II might block pathologic immune responses associated with these molecules while sparing normal immune responses that can be mediated by other MHA II molecules. This might be achieved either with mAb to selected MHA II or with other agents designed to bind, and inhibit, disease-associated epitopes on MHA II molecules.

Summary

Current pharmacologic approaches to immune suppression leave much to be desired. The prevention of allograft rejection and the suppression of autoimmunity generally require treatment with corticosteroids or cytotoxic drugs, or both, which may not be sufficiently effective and which frequently cause serious immediate and long-term complications. With the advent of monoclonal antibody technology, it has become possible to identify and selectively inhibit distinct elements in the immune system that contribute to pathologic immune responses. This achievement has led to new therapeutic strategies that may be safer and more effective than the immunosuppressive therapies currently available. Many of these strategies focus on subsets of T cells because of the critical importance of T cells in immune responses. Monoclonal antibodies directed against CD4 + T cells, T-cell activation antigens, and T-cell receptor families have all shown promise in animal models and, in some cases, in preliminary human trials. The challenge now is to translate this promise into practical new forms of immunosuppressive therapy.

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Tryptophan-Induced Eosinophilia-Myalgia Syndrome

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Eight patients who became ill while taking tryptophan had myalgia, fatigue, rash, fever, edema, alopecia, arthralgias, diminished joint motion, skin tightening, muscle cramping, and distal paresthesias. Three had shortness of breath, and one had pulmonary hypertension. Laboratory abnormalities included peripheral eosinophilia, leukocytosis, thrombocytosis, raised erythrocyte sedimentation rate, and elevated serum levels of aldolase, lactate dehydrogenase, and liver enzymes. Of 4 chest radiographs, 3 were abnormal. Of 5 skin and muscle biopsies, 4 showed sclerosis or mixed inflammatory cell infiltration of the dermis, subcutis, and fascia. Eosinophils were often present, but vasculitis was absent. Muscle inflammation was minimal. We conclude that the "eosinophilia-myalgia syndrome" is related to the ingestion of tryptophan and that abnormalities in the secretion of lymphokines may be important in its pathogenesis.

(Criswell LA, Sack KE: Tryptophan-induced eosinophilia-myalgia syndrome. West J Med 1990 Sep; 153:269-274)

In October 1989, the New Mexico Department of Health and Environment received reports of illness in patients taking tryptophan tablets.[1] A striking component in all cases was profound eosinophilia. Common clinical features included myalgia, weakness, fever, arthralgia, dyspnea, rash, extremity edema, and pneumonia. Other features were congestive heart failure, cardiac arrhythmias, hypoxemia, liver enzyme abnormalities, muscle enzyme elevations, bone marrow eosinophil hyperplasia, and perivascular inflammatory infiltrates (with relative muscle sparing) on histologic examination of muscle.[2] No patient had an associated infection or neoplasm.

The Centers for Disease Control (CDC) coined the term "eosinophilia-myalgia syndrome" (EMS) and recommended the following case definition:

- The presence of an eosinophil count of 1.0×10^9 cells per liter or greater;
- Myalgias severe enough to interfere with the performance of a patient's usual daily activities; and
- The exclusion of infectious or neoplastic illnesses that might account for the first two findings.[3-5]

By January 1990, a total of 1,046 cases of EMS (including 7 deaths) had been reported to the CDC.[6] Three months earlier, in November 1989, the Food and Drug Administration (FDA) advised the public against consuming tryptophan tablets.

In this report, we review the possible pathogenesis of this syndrome and describe eight new illustrative cases.

Reports of Cases

Patient 1

A 42-year-old woman began taking tryptophan six to seven years ago for insomnia. In late 1988 she increased her daily dose from 1,000 to 2,000 mg. In August 1989, generalized fatigue developed, followed by myalgia in her thighs and upper arms. Turning in bed caused her excruciating pain. A faint, pink, pruritic rash appeared on her abdomen and trunk and spread to her shoulders and thighs. She also noted low-grade fevers, swelling of the face, eyelids, and ankles, and dyspnea on exertion.

In September she received dicloxacillin sodium for a presumed staphylococcal infection, but she did not improve. Her physician noted peripheral eosinophilia. Laboratory studies elicited the following values: leukocyte count 22.4×10^9 per liter (eosinophils 0.40),* platelet count 542×10^9 per liter, serum aldolase 13.8 units per liter, and antinuclear antibody titer +1:640 (homogeneous). A specimen of bone marrow revealed eosinophilic hyperplasia; a muscle biopsy specimen showed mixed inflammatory cell infiltration (including numerous eosinophils) in the subcutis and dermis and surrounding several septal nerves in the subcutis.

Treatment with several nonsteroidal anti-inflammatory drugs and acetaminophen was ineffective, but a regimen of prednisone, 60 mg per day, caused prompt improvement. Reducing the dose to 20 mg per day caused a transient flare in symptoms, which resolved within two weeks. She discontinued tryptophan after hearing reports of its toxicity.

On presentation to the University of California, San Francisco, Medical Center in December 1989, she was taking 15 mg of prednisone per day and complained of cramping in her calves, burning pains in her toes, and diminished range of motion in her ankles.

The findings of a physical examination were unremarkable except for a region of firm subcutaneous nodularity in the calves, brawny induration and peau d'orange in both lower legs, diminished range of motion in the ankles, and tenderness in the muscles of her upper arms and thighs. Additional laboratory studies showed a leukocyte count of 13.1×10^9 per liter (eosinophils 0.06) and normal levels of serum immunoglobulin E.

She is currently taking prednisone in low doses. Her ankle range of motion has improved, but mild myalgia and subcutaneous nodularity in her calves persist.

Patient 2

In August 1988, this patient, a 40-year-old woman, began taking tryptophan, 667 to 3,300 mg per day, for insomnia. Three months later she became fatigued. Serum chemistry levels and thyroid function studies were normal, but her leukocyte count was 9.5×10^9 per liter (eosinophils 0.21). In January 1989 she noted diffuse alopecia and low-grade fever (38.1°C). Examination of a peripheral blood film showed 0.04 eosinophils; an erythrocyte sedimentation rate was 12 mm per hour. The following month she had

*Throughout this article, eosinophil counts are expressed as a fraction of 1.

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ABBREVIATIONS USED IN TEXT

CDC = Centers for Disease Control
$D_L$co = diffusing capacity of carbon monoxide
EMS = eosinophilia-myalgia syndrome
FEV_1 = forced expiratory volume in 1 second
FVC = forced vital capacity

diffuse muscle and joint aches, swelling of her hands and feet, and a "burning" sensation in her distal extremities. A laboratory evaluation revealed the following values: leukocyte count 9.8 × 10^9 per liter (eosinophils 0.34), hemoglobin 121 grams per liter, erythrocyte sedimentation rate 40 mm per hour, and normal urinalysis. Therapy with nonsteroidal anti-inflammatory drugs was ineffective, and in March 1989 she was referred to our facility.

She reported a rash on her abdomen but said she did not have fevers, Raynaud's phenomenon, dry eyes or mouth, or respiratory or abdominal symptoms. She had a history of depression and a false-positive VDRL test. Medications included a combination drug of propoxyphene napsylate and acetaminophen and chloral hydrate, cyclobenzaprine hydrochloride, naproxen sodium, multivitamins, and tryptophan, 670 to 3,300 mg per day.

On physical examination she had diffuse muscle tenderness, swelling and reduced flexion of the metacarpophalangeal and proximal interphalangeal joints, and diminished range of motion in the ankles. A leukocyte count was 11.9 × 10^9 per liter (eosinophils 0.29), and an erythrocyte sedimentation rate was 45 mm per hour; a serum hemoglobin level and platelet count were normal. A full-thickness skin biopsy specimen showed inflammation of the fascia with an infiltration of eosinophils, consistent with eosinophilic fasciitis.

The patient received prednisone, 15 mg per day, and within two weeks noted a decrease in her distal extremity swelling. She continued taking tryptophan. Over the ensuing six months, the swelling diminished in the lower extremities but skin thickening progressed, along with further loss of ankle motion. She had severe burning pain and paresthesias in her feet. In October, an increased dose of prednisone to 45 mg per day yielded no improvement. Her erythrocyte sedimentation rate ranged from 3 to 46 mm per hour and an absolute eosinophil count from 0 to 0.55 × 10^9 per liter (normal 0.15 to 0.30). She stopped taking tryptophan in November 1989 after learning of the eosinophilia-myalgia syndrome. In December she received hydroxychloroquine sulfate, 200 mg twice a day, and gradually discontinued prednisone. Her muscle cramping has diminished, but her other symptoms are unchanged.

Patient 3

In May 1989 the patient, a 62-year-old woman, began taking tryptophan, 500 to 1,000 mg per day, for insomnia. In August she noted generalized myalgia, followed in two weeks by diffuse pruritus. She said she did not have fever, skin rash, morning stiffness, joint pain or swelling, or abdominal complaints, but she observed diminished joint range of motion and mild dyspnea on exertion. She discontinued tryptophan in October after hearing reports of its toxicity. In November her leukocyte count was 11.8 × 10^9 per liter (eosinophils 0.37), an erythrocyte sedimentation rate was 19 mm per hour, and liver enzyme levels were twice normal. A chest radiograph showed "streaky infiltrates." Her medical history was notable for psoriasis. Her only medication was estrogen.

Physical examination in mid-November 1989 showed slight right axillary adenopathy, mild lower leg edema, generalized muscle tenderness (especially trapezius muscles), and right knee crepitus.

Laboratory studies elicited a peripheral eosinophilia (0.07), persistent liver enzyme elevation, and a platelet count of 600 × 10^9 per liter. A week later, she began taking prednisone, 10 mg per day, increasing the dose three days later to 20 mg when she did not improve. Ten days later she felt better, and by mid-December she had reduced her prednisone dosage to 7 mg per day. She continued to have mild lower leg edema and diffuse back tenderness. Liver enzyme levels and a total eosinophil count were normal. By February 1990 she was no longer taking prednisone. Persisting symptoms were moderate myalgia, pruritus, pretibial edema, and skin tightening.

Patient 4

The patient, a 32-year-old woman, began taking tryptophan, 1,400 to 2,000 mg per day, in 1988 for insomnia. In September 1989, fever, chills, headache, malaise, and fatigue developed, followed by muscle stiffness in her lower extremities and then in her back and arms. Taking ibuprofen, 600 mg three times a day, was ineffective. In October she had "back spasms and knots," worsening stiffness, and fatigue.

Laboratory studies yielded the following values: serum aldolase 15.1 units per liter, lactate dehydrogenase 857 units per liter (normal < 600), elevated liver enzymes, leukocyte count 14.1 × 10^9 per liter (eosinophils 0.34), and antinuclear antibody titer +1:640 (speckled pattern). An electrocardiogram was unremarkable except for sinus tachycardia. A chest radiograph showed borderline cardiomegaly.

In November 1989 palpitations developed, and the patient had several erythematous maculopapular lesions on her abdomen, trunk, and thighs. She discontinued tryptophan after hearing reports of its toxicity. The family history was notable for "skin lupus" in her mother.

On physical examination in November 1989 the patient was in a wheelchair, was thin, and appeared ill. She had several small red papules on her abdomen and diffuse muscle tenderness, particularly of the thighs, calves, and shoulders. Biopsy specimens of skin and muscle showed normal dermis and muscle, inflammation and edema of the fascia, sclerosis of the mid and deep dermis, and perivasculitis with rare eosinophils. A regimen of prednisone, 20 mg three times a day, induced a pronounced decrease in myalgia; however, she had incapacitating muscle cramps (diaphragm, legs, hands) develop that were inadequately controlled with diazepam and carbamazepine. Her muscle cramps diminished as the prednisone dose was tapered. While taking prednisone, 20 mg per day, she had no peripheral eosinophilia; serum aldolase and liver enzyme levels were normal. She is currently receiving 7 mg per day of prednisone and has mild myalgia.

Patient 5

A 57-year-old woman began taking tryptophan, 2,500 to 3,500 mg per day, in July 1988 for insomnia and anxiety. A month later she decreased her daily dose to 2,000 mg. In October 1988, fatigue, dyspnea on exertion, and a minimally productive cough developed. A chest radiograph showed diffuse interstitial prominence, and pulmonary function studies showed the following blood gas values (with the patient breathing room air): pH 7.49, Pco_2 25 mm of mercury, Po_2 62 mm of mercury. Her carbon monoxide

diffusing capacity (D_Lco) was 45% of predicted, the forced expiratory volume in 1 second (FEV_1) was 89% of predicted, and the forced vital capacity (FVC) was 73% of predicted. A second chest radiograph in November 1988 was again abnormal, but the infiltrates cleared by January 1989. Pulmonary symptoms persisted, and she had pain, paresthesias, and skin thickening in both lower extremities. She discontinued tryptophan in February 1989. Four months later, an angiogram showed 90% stenosis of the left common iliac artery; cardiac catheterization revealed pulmonary hypertension (pulmonary artery pressure 71/23 mm of mercury), nonocclusive coronary artery disease, normal aortic and mitral valves, and a normal left ventricular ejection fraction. A ventilation-perfusion scan and pulmonary angiogram were normal.

The skin changes progressed to her thighs, buttocks, lower back, and lower extremities. A deep skin biopsy specimen in July 1989 showed dermal sclerosis, infiltration of lymphocytes, plasma cells, and eosinophils between the deep dermis and subcutis, and normal skeletal muscle. These changes were consistent with the diagnosis of morphea or scleroderma. Laboratory studies showed an antinuclear antibody titer of +1:160, a leukocyte count of 14.6 $\times 10^9$ per liter (eosinophils 0.26), and the absence of antibodies to Scl 70 and centromere. The systolic pulmonary artery pressure by echocardiogram was estimated to be 80 to 85 mm of mercury. A regimen of prednisone, 20 mg per day, and penicillamine, 250 mg per day, was started in August 1989. Dyspnea and skin thickening progressed, but she did not have fever, Raynaud's phenomenon, dysphagia, or gastrointestinal symptoms.

The patient was referred to our facility in early September 1989. She gave a history of hypothyroidism, ichthyosis, heavy cigarette use, and previous alcohol abuse. Medications included prednisone (10 mg per day) penicillamine (250 mg per day) levothyroxine, estrogen, propoxyphene-acetaminophen, erythromycin, isosorbide dinitrate, and sublingual nitroglycerin.

On physical examination she had generalized skin changes of ichthyosis, bilateral foot swelling, and marked skin thickening and tightening over the lower extremities, forearms (sparing the hands), abdomen, chest, back, buttocks, and lower breasts. A cardiac examination revealed a widely split and accentuated S_2, an S_4 gallop, and a grade 2/6 systolic murmur at the lower left costal margin. An electrocardiogram showed normal sinus rhythm, right axis deviation, and evidence of right ventricular hypertrophy.

Penicillamine was discontinued and the prednisone dose was increased to 60 mg per day. Her dyspnea progressed rapidly, however, and she underwent Swan-Ganz catheterization in December 1989. The initial pulmonary arterial pressure was 82/31 mm of mercury (mean, 49), which did not improve with vasoactive medications. The leukocyte count was 14.1 $\times 10^9$ per liter with no eosinophilia. A chest radiograph showed right ventricular hypertrophy, dilated pulmonary arteries, and no infiltrates or effusions. Blood gas values with the patient breathing room air were as follows: pH 7.42, Pco_2 36 mm of mercury, and Po_2 79 mm of mercury. The FEV_1 was 77% of predicted, FVC 87% of predicted, and D_Lco 65% of predicted. A computed tomographic scan of the thorax with high-resolution thin sections showed "focal areas of patchy consolidation . . . without interstitial disease."

By February 1990 she was taking 10 mg of prednisone and 500 mg of penicillamine per day. Her lower extremity pain, skin tightening, and pulmonary symptoms were unchanged.

Patient 6

The patient, a 42-year-old woman, began taking tryptophan, 500 to 1,000 mg per day, in 1987 for insomnia. In early 1989, she had generalized fatigue develop, followed by easy fatigability in her arms and legs. In May 1989 laboratory studies showed a leukocyte count of 8.3 $\times 10^9$ per liter (eosinophils 0.16), elevated liver enzymes and lactate dehydrogenase levels, and an antinuclear antibody titer of less than 1:40. By June, her liver enzyme levels were normal but eosinophilia persisted. In September pain occurred in her knees, hips, and low back, accompanied by morning stiffness and swelling in the feet. These symptoms were partially relieved by the administration of ibuprofen, 400 mg four times a day. She discontinued tryptophan in November after hearing reports of its toxicity. By December, her total eosinophil count was 0.739 $\times 10^9$ per liter. She complained of mild alopecia and a red rash on her feet but did not have Raynaud's phenomenon or sicca symptoms. Her family history included diabetes mellitus and thyroid disease but no rheumatic illnesses.

In January 1990 she came to this center, where on physical examination she had slight brown discoloration over the calves and right lateral ankle, without definite skin thickening. Her forearms and lower legs were tender, and the metacarpophalangeal and elbow joints were hypermobile. She continues to take ibuprofen, 400 mg four times a day, and has moderate myalgia.

Patient 7

The patient, a 60-year-old woman, began taking tryptophan, 1,000 to 1,500 mg per day, for insomnia in 1987. In September 1989 generalized muscle and joint pain developed for which she took piroxicam. A severe urticarial reaction occurred, and she received a brief course of prednisone. Low-grade fever ensued, accompanied by muscle weakness and swelling of the arms and legs.

Laboratory studies in October 1989 elicited the following values: leukocyte count 11.9 $\times 10^9$ per liter (eosinophils 0.14), hemoglobin 134 grams per liter, and platelet count 333 $\times 10^9$ per liter. A month later, the results of a physical examination were unremarkable. She discontinued tryptophan because of reports of toxicity but noted no immediate relief of symptoms. Her leukocyte count in November was 11.3 $\times 10^9$ per liter (eosinophils 0.12). Diffuse alopecia occurred in December. The erythrocyte sedimentation rate was 32 mm per hour, leukocyte count was 12.1 $\times 10^9$ per liter (eosinophils 0.19), and her hemoglobin concentration and platelet count were normal.

Her medical history was notable for hypothyroidism diagnosed in 1987. Other medications included levothyroxine, estrogen, and enteric-coated aspirin. The family history revealed pernicious anemia in her mother.

On physical examination in January 1990 she had diffuse scalp alopecia, dry skin, lower extremity edema, and muscle tenderness (especially in the lower legs and upper arms). Mild myalgia persists.

Patient 8

A 79-year-old woman began taking tryptophan, 3,000 to 4,000 mg per day, in 1981 for migraine headaches. In 1984 pain and swelling of her right foot developed, and she was told she had a positive "lupus test." Symptoms resolved when she took 12 aspirin tablets per day. In 1988 she noted bilateral knee pain and swelling, aching in her hips, thighs, and thumbs, and prolonged morning stiffness. These symptoms continued despite the regular use of aspirin. For five years she has had diffuse alopecia, and she had dryness of

her mouth, eyes, and vagina. Her medical history revealed rheumatic fever and hypothyroidism (possibly due to Hashimoto's thyroiditis). Medications at the time of evaluation included tryptophan, 3,000 mg to 4,000 mg per day, levothyroxine, estrogen, and aspirin, 12 tablets per day.

A physical examination in late December 1989 was notable for slightly dry skin, diffuse scalp alopecia, diminished salivary pool with gingival erosion, and tenderness of the upper trapezius and gluteal muscles. She had stasis pigmentary changes over her left foot and trace lower extremity edema. On neurologic examination she had a depressed affect and diminished lower extremity deep tendon reflexes.

Laboratory studies showed a leukocyte count of 10×10^9 per liter (eosinophils 0.01) and an antinuclear antibody titer of 1:80 (diffuse). She discontinued tryptophan in December. Her symptoms remain unchanged.

Summary of Cases

Most of the patients were previously healthy and physically active. They were all women (mean age, 52 years). In the first 30 cases of the eosinophilia-myalgia syndrome reported, there were 17 women and 13 men. Our patients' mean daily dose of tryptophan was 1,800 mg (range, 750 to 3,500 mg) taken for an average of 39 months (range, 8 to 108 months). We saw no relationship between the severity of illness and either the daily dose of tryptophan or the duration of its consumption. The discontinuation of tryptophan has not led to rapid recovery.

Prominent clinical features in our patients were fatigue, skin rash, myalgia, arthralgia, and peripheral edema (see Table 1). Other, sometimes dominant, symptoms included muscle cramping—often exacerbated by corticosteroid treatment—diminished joint range of motion, skin tightening and thickening, alopecia, burning pain and paresthesias, and shortness of breath.

Striking peripheral eosinophilia occurred in all but one patient. On discontinuing tryptophan, the eosinophilia usually persisted until the institution of a regimen of prednisone. In one patient (patient 3), total eosinophil counts fell from 4.4×10^9 to 0.6×10^9 per liter before corticosteroid therapy was started. Serum aldolase levels were often above normal without concomitant creatine kinase elevations (Table 2). The findings of muscle and skin biopsies were abnormal in four of five patients. Typical abnormalities were sclerosis or mixed inflammatory cell infiltration of the dermis, subcutis, and fascia with relative sparing of muscle. Eosinophils were often present, but vasculitis was absent.

Patient 8 did not have documented eosinophilia and thus did not meet the CDC case definition of EMS. This patient, however, had clinical features similar to those in our other patients. Therefore, until the role of the eosinophil in this syndrome is clearly established, it may be premature to exclude patients who do not have peripheral eosinophilia at the initial presentation.[2]

The response to the cessation of tryptophan was slow, and in some patients chronic symptoms developed. Administering nonsteroidal anti-inflammatory drugs or low doses of prednisone was usually ineffective. High-dose steroid therapy produced a dramatic decrease in myalgias, but severe muscle cramping necessitated dose reduction. Two patients are receiving hydroxychloroquine sulfate and penicillamine because of progressive skin thickening and pulmonary hypertension unresponsive to high doses of corticosteroids. These agents have not yet produced demonstrable improvement.

Discussion

The cause of EMS is unknown. Attempts to isolate a contaminant or to implicate particular brands or lots of

TABLE 1.—*Selected Clinical Features in 8 Patients With the Eosinophilia-Myalgia Syndrome According to Frequency**

Patient	Muscle Pain	Fatigue	Edema	Rash	Joint Pain	Decreased Joint ROM	Fever	Alopecia	Skin Tightening	Muscle Cramp	Burning Pain	Shortness of Breath
1	Yes	Yes	Yes	Yes	No	Ankles	Yes	No	Yes	Yes	Feet	Yes
2	Yes	Yes	Yes	Yes	Yes	Ankles	Yes	Yes	Yes	Yes	Feet	No
3	Yes	No	Yes	No	No	Yes	No	No	No	No	No	Yes
4	Yes	Yes	No	Yes	No	Yes	Yes	No	No	Yes	No	No
5	Yes	Yes	Yes	Yes	No	No	No	No	Yes	No	Legs	Yes
6	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	No	No	No
7	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	No	No
8	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	No	No	No

ROM = range of motion

*The features on the left occur most frequently and on the right least frequently.

TABLE 2.—*Available Laboratory Data in 8 Patients With the Eosinophilia-Myalgia Syndrome*

Patient	Leukocyte Count × 10^9/liter	Eos *	Plotelets × 10^9/liter	Hemoglobin, groms/liter	Aldolose, units/liter†	ESR, mm/h	LDH, units/liter	Liver Enzymes	ANA Titer	Urine	Chest X-roy Film	Muscle Biopsy
1	22.4	0.52	542	139	13.8	5	414	High	1:640	Normal	Normal	Abn
2	9.8	0.34	252	121	...	46	...	Normal	<1:40	Normal	...	Abn
3	11.8	0.37	634	126	13.0	13	329	High	...	...	Abn	Normal
4	10.6	0.42	575	127	15.5	27	359	High	1:640	Normal	Abn	Abn
5	14.6	0.26	359	144	...	...	...	Normal	1:320	Abn	Abn	Abn
6	8.3	0.16	395	119	...	8	202	High	<1:40	...	...	...
7	12.1	0.19	381	131	...	32	...	Normal	1:40	Normal	...	...
8	10.0	0.01	...	145	...	2	...	Normal	1:80	Normal	...	...

Abn = abnormal, ANA = antinuclear antibody, Eos = eosinophils, ESR = erythrocyte sedimentation rate, LDH = lactate dehydrogenase

*Eosinophil counts are expressed as a fraction of 1.
†All available serum creatine kinase values were normal.

tryptophan have failed. In one report, however, 98% of EMS patients compared with approximately 40% of controls had used tryptophan produced by a particular manufacturer.[7] Tryptophan itself has been implicated in scleroderma-like illnesses. In 1958 sclerodermatous skin lesions were noted in patients with metastatic carcinoid tumors. Plonk and Feldman subsequently described "carcinoid arthropathy" in five consecutive patients with the carcinoid syndrome.[8] They noted prominent complaints of arthralgias, primarily in the fingers, hands, and wrists, and unique radiographic changes in the fingers and hands of several patients. In addition, they described a patient with progressive systemic sclerosis, arthralgias in the hands, and radiographic changes identical to those in the carcinoid patients. Treatment of one of their patients with parachlorophenylalanine, an inhibitor of tryptophan hydroxylase activity and serotonin synthesis, caused a resolution of arthralgias and joint stiffness. Price and co-workers described an abnormality of tryptophan metabolism in a young girl with scleroderma and in 21 other members of her family.[9] This was distinct from previously described heritable abnormalities of tryptophan metabolism based on the pattern of urinary tryptophan metabolites. South African miners with scleroderma have similar abnormalities of tryptophan metabolism.[10] Fries and associates hypothesize that serotonin or other tryptophan metabolites induce capillary permeability and tissue edema.[11] In 1980 Sternberg and colleagues described a scleroderma-like illness that developed during treatment with L-5-hydroxytryptophan and carbidopa for intention myoclonus.[12] They implicated high plasma serotonin and kynurenine levels as possible causes of scleroderma. A recent report describes the resolution of musculoskeletal symptoms in three patients with the carcinoid syndrome who received a somatostatin analogue.[13]

Eosinophil granule-associated proteins could also produce some of the tissue damage of EMS. Major basic protein is toxic to several mammalian tissues including intestine, spleen, skin, and peripheral blood mononuclear cells.[14] Furthermore, major basic protein is a possible cause of lung tissue injury in chronic eosinophilic pneumonia.[15] Eosinophil-derived neurotoxin disrupts neurons and myelinated axons,[16-19] and eosinophil cationic protein damages cardiac cell membranes and mitochondrial enzyme systems.[20,21] Eosinophils are thought to cause the organ damage seen in the idiopathic hypereosinophilic syndrome, a disorder with some similarities to EMS.[22]

Peripheral eosinophilia accompanies other musculoskeletal diseases. These include disseminated eosinophilic collagen disease,[23] eosinophilic fasciitis,[24] eosinophilic myositis, and eosinophilic perimyositis. In 1988 Lakhanpal and co-workers described a case of severe myalgia, bronchial asthma, pulmonary infiltrates, peripheral eosinophilia, and eosinophilic perimyositis in a 61-year-old woman.[25] Treatment with corticosteroids produced notable symptomatic benefit. They considered this the first case of systemic eosinophilic disease and perimyositis, but close scrutiny of the patient's medical history reveals the ingestion of "numerous self-prescribed vitamins and mineral supplements" subsequently found to include tryptophan tablets. In reality, this may be the first report of EMS.

Many features of the eosinophilia-myalgia syndrome resemble the toxic oil syndrome. This illness was linked to the ingestion of adulterated rapeseed oil[26] and within the first year of its description had resulted in 315 deaths out of an estimated 19,828 cases.[26,27] Prominent clinical features included fever, chills, headache, pruritus, cough, chest pain, gastrointestinal symptoms, and muscle pain, cramping, and weakness. Physical examination revealed skin rash, alopecia, tachycardia, hepatosplenomegaly, lymphadenopathy, muscle atrophy, limb contractures, and depressed deep tendon reflexes. Laboratory features were leukocytosis, eosinophilia, and elevations of the erythrocyte sedimentation rate, liver enzyme levels and serum aldolase concentration. Chest radiographs showed interstitial infiltrates. The severity of illness did not appear to correlate with the extent of exposure to the tainted oil.

Three years after the initial outbreak of the toxic oil syndrome, it was apparent that some patients had a chronic, progressive illness. In 1986 Alonso-Ruiz and associates described the cases of 32 patients with the syndrome in whom Raynaud's phenomenon, scleroderma-like skin changes, livedo reticularis, joint contractures, myalgias, muscle cramps, peripheral neuropathy, sicca syndrome, pulmonary hypertension, and mild liver disease had developed.[28] Tissue biopsies documented severe dermal fibrosis and obliterative arteriopathy. Gómez-Sánchez and colleagues recently described seven cases of the toxic oil syndrome in patients who died as a result of severe pulmonary hypertension.[29] Pulmonary histologic findings were similar to those described in primary pulmonary hypertension. Vicario and co-workers described an association of haplotypes HLA-DR3, DR4, and DR3/DR4 in a group of patients with chronic symptoms of the toxic oil syndrome.[30] These haplotypes are common in patients with autoimmune diseases.

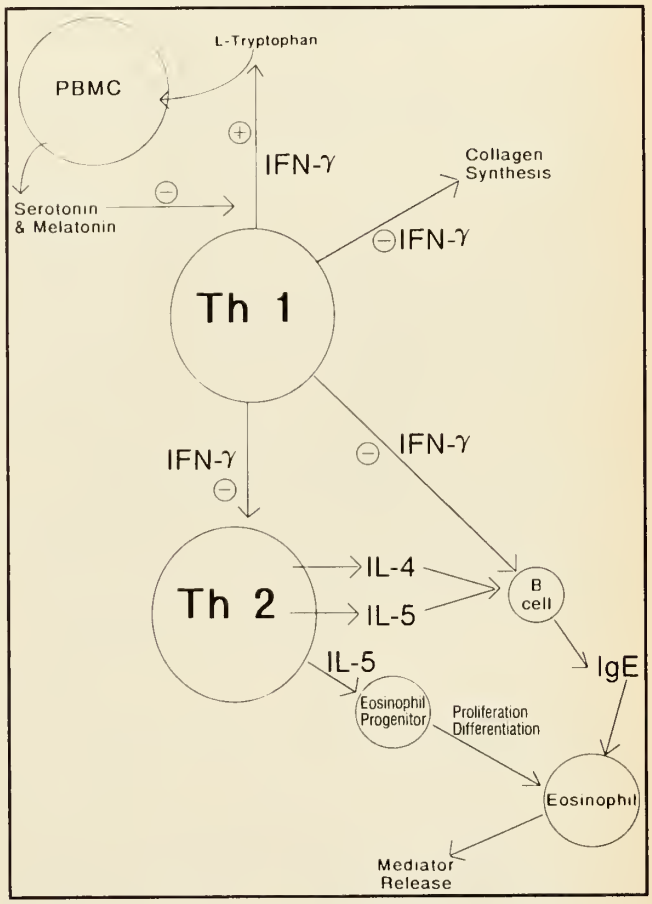

Figure 1.—Uptake of tryptophan by peripheral blood mononuclear cells (PBMC) results in secretion of serotonin and melatonin through intracellular metabolism. These indoleamines inhibit interferon-gamma (IFN-γ) synthesis, which could lead to uncontrolled collagen synthesis and peripheral eosinophilia by the pathway shown. IL-4 = interleukin-4, IL-5 = interleukin-5, Th 1 = T-helper cell subset 1, Th 2 = T-helper cell subset 2

Thus, the toxic oil syndrome is a chemically induced disorder that has many similarities to eosinophilic fasciitis, systemic sclerosis, and EMS. Other substances that can induce a scleroderma-like illness include vinyl chloride, silica dust, organic solvents, epoxy resins, paraffin, silicon (as used in breast augmentation), and drugs such as bleomycin, carbidopa, and 5-hydroxytryptophan.[31-33] The last two drugs cause abnormalities of tryptophan metabolism.

Patients typically take tryptophan for insomnia, depression, and the premenstrual syndrome. Until recently, this substance was readily available in health food stores and supermarkets. Most of our patients used more than one brand of tryptophan purchased at different times and locations. Many of these preparations could come from the same manufacturer and could contain a toxic contaminant. We think, however, that tryptophan itself could produce this syndrome. In view of the known relationship between tryptophan and various lymphokines,[34-58] we suggest that an inhibition of interferon-gamma synthesis by tryptophan metabolites (serotonin and melatonin) could result in uncontrolled collagen synthesis and peripheral eosinophilia (Figure 1). Careful observation of patients with EMS should provide further clues to its pathogenesis and a rationale for appropriate treatment.

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Articles

Pleuropulmonary Manifestations of Hepatic Amebiasis

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Pleuropulmonary manifestations of hepatic amebiasis occurred in 30 patients; 18 (60%) presented with at least 1 pulmonary complaint and 10 (33%) had multiple pulmonary symptoms. In 14 patients (47%), abnormalities were found on examination of the chest. In 16 chest roentgenograms (53%), there was at least 1 abnormality: right-sided pleural effusion (9 patients) and elevated right hemidiaphragm (8 patients) were the most common. All patients were treated with metronidazole (Flagyl) and had resolution of the amebic liver abscess and pulmonary disease. Pleuropulmonary disease is a common complication of amebic liver abscess. The clinical presentation and chest roentgenograms are virtually diagnostic and obviate the need for invasive procedures to confirm the diagnosis. Pleuropulmonary disease resolves with amebicidal treatment of the hepatic abscess.

(Lyche KD, Jensen WA, Kirsch CM, et al: Pleuropulmonary manifestations of hepatic amebiasis. West J Med 1990 Sep; 153:275-278)

Human infection due to *Entamoeba histolytica* is common in third-world countries. Amebiasis, however, is "neither tropical nor exotic" and can occur anywhere.[1] Cases of amebiasis are frequently seen in the United States because of the large number of immigrants from endemic areas.

Intestinal disease is the most common manifestation of amebiasis, and infection of the liver through the portal vein is the most common extraintestinal site of involvement.[2] The right lung and pleural space are frequently affected by amebic liver abscess, perhaps because of their proximity to the liver.[3] The exact incidence of pulmonary involvement complicating hepatic amebiasis is unknown, but some studies suggest that clinical or radiographic abnormalities of the chest occur in about 50% of cases.[2,4-6]

To define the frequency and nature of pulmonary complications due to hepatic amebiasis, we reviewed all cases of amebic liver abscess seen at the Santa Clara Valley Medical Center in San Jose, California, during an eight-year period.

Methods

From 1981 to 1988, amebic liver abscess was diagnosed in 30 patients at the Santa Clara Valley Medical Center. Cases were identified by reviewing charts of all patients with a discharge diagnosis of amebic liver abscess. Each chart was reviewed using a standardized data-collection sheet to record pertinent clinical features, laboratory test results, radiographic studies, and the clinical course.

Serum indirect hemagglutination antibody (IHA) titers (Boehringer Diagnostics, Indianapolis, Ind) were considered positive if the initial titer was 1:128 or higher or if there was a fourfold rise from specimens taken during the acute to convalescent phases. A computed tomographic (CT) scan or an ultrasound examination of the liver showing intrahepatic defects compatible with an abscess was considered consistent with an amebic liver abscess.

Clinical improvement with metronidazole therapy was defined as a resolution of or improvement in any or all of the following when present: fever, right upper quadrant pain, pleuritic pain, leukocytosis, or liver chemistry values (serum aminotransferase, alkaline phosphatase, and bilirubin).

The following three groups comprise clinical features considered diagnostic of amebic liver abscess:

Group 1. Entamoeba histolytica trophozoites are identified in a specimen of liver aspirate.

Group 2. An IHA serologic test is positive, and an ultrasonogram or CT scan shows findings compatible with a liver abscess. (In one patient, the diagnosis was based on a positive IHA test in the setting of a lidofenin (HIDA) scan that showed a photopenic area in the liver consistent with liver abscess.)

Group 3. Trophozoites or cysts are identified in a stool specimen, the findings of an ultrasonogram or CT scan are compatible with liver abscess, and the patient has a clinical response to treatment with metronidazole.

We reviewed all chest roentgenograms and interpreted them as either normal or as showing one or more of the following abnormalities:

- Elevated right hemidiaphragm, defined as an elevation of the dome of the right hemidiaphragm 3.0 cm or more above the dome of the left hemidiaphragm.[7(p156)]
- Pleural effusion, defined as one or all of the following: blunting of the right costophrenic angle, a meniscus on a posteroanterior film, or layering of fluid on a decubitus film.
- Infiltrate or atelectasis.

Results

Identifying characteristics of the patients studied are shown in Table 1. The patients' ages ranged from 2 to 64 years with a mean of 31 years. Two thirds were in their third and fourth decades of life. All but one were male, and all of the cases occurred in immigrants from third-world countries including Mexico, Vietnam, and India. At least 73% of the cases (22) occurred in persons who had been in this country for less than two years (Table 1). Two patients fit

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ABBREVIATIONS USED IN TEXT

CT = computed tomographic
IHA = indirect hemagglutination antibody

the diagnostic criterion of group 1, 27 of group 2, and 1 of group 3 (see Methods).

The chief complaints of the 30 patients are shown in Table 2. The majority (25, or 83%) presented with right upper quadrant or other abdominal pain. Of the 15 patients who presented with right upper quadrant pain, 11 (73%) had pulmonary signs on physical examination and 8 (53%) had an abnormal chest roentgenogram. Two of the 30 patients (7%) presented primarily with thoracic symptoms: one had cough and the other right shoulder pain. Table 3 lists the symptoms and signs of all 30 patients. Overall, 18 patients (60%) presented with at least one pulmonary complaint such as cough, sputum production, pleuritic pain, shoulder pain, or shortness of breath; 10 patients (33%) had two or more of these symptoms. Of the 18 patients with pulmonary symptoms, 11 (61%) had signs of pulmonary involvement on examination and 9 (50%) had abnormal chest roentgenograms.

Four patients were initially not suspected of having amebiasis and were misdiagnosed as having other disorders. Two were admitted to the surgical service with the diagnosis of acute abdomen. The diagnosis of hepatic amebiasis was not considered until imaging studies of the right upper quadrant showed a hepatic abscess. One patient was treated with ampicillin for several days before hospital admission for a presumed urinary tract infection until an abdominal ultrasonogram showed a liver abscess. Another patient received erythromycin orally for four days for pneumonia until worsening right upper quadrant pain led to the discovery by ultrasonography of a liver abscess.

Fever and abdominal tenderness were found in 90% of the patients. Hepatomegaly, defined as a total liver span of 11 cm or more, was found in 14 patients. Of those with hepatomegaly, 10 (72%) had pulmonary symptoms and 7 (50%) had physical signs localized to the chest and abnormal chest roentgenograms.

Overall, 14 patients (47%) had abnormal physical findings on examination of the chest, including decreased breath sounds, signs of consolidation, dullness on percussion, crackles, or a pleural rub. Six patients (20%) had evidence of two or more of these signs. Of the 14 patients with pulmonary signs on examination, 11 (78%) had abnormal chest roentgenograms.

The results of admission chest roentgenograms in all 30 cases are shown in Table 4. While 16 (53%) had at least one abnormality, 14 films (46%) were completely normal. The most common findings were an elevated right hemidiaphragm seen in eight patients (27%) and a right-sided pleural effusion seen in nine patients (30%) (Figure 1). In four patients (13%), the chest films showed evidence of right basilar atelectasis. Of note, multiple radiographic abnormalities were seen in four patients (13%). Follow-up chest roentgenograms were obtained in 17 patients from 1 to 20 days after presentation (mean, 4 days). A resolution or improvement was seen in 2 patients, persistent abnormality in 12, and a new radiographic abnormality in 3 (right pleural effusion in 2 and elevated right hemidiaphragm and pleural effusion in 1).

Three patients underwent thoracentesis for their pleural effusions, two for diagnostic purposes and the other to alleviate the patient's severe dyspnea due to a large pleural effusion. This patient also required chest-tube insertion to drain the pleural effusion and relieve dyspnea. The exudates from all three patients were characterized by a protein content of 53 grams per liter or more and a pleural fluid-serum ratio of lactate dehydrogenase greater than 0.6. Microbiologic studies done on all three specimens were negative, including Gram's stain and cultures for bacteria, as well as

TABLE 1.—*Demographic Characteristics of 30 Patients With Pleuropulmonary Manifestations of Hepatic Amebiasis**

Characteristic	*Patients, No.*
Sex, male	29
Race or ethnicity	
Hispanic	23
Vietnamese	6
Indian	1
Years in United States	
<1	15
1-2	7
>2	6
Unknown	2

*Patients' ages were 2 to 64 years (mean, 31).

TABLE 2.—*Chief Complaints of 30 Patients With Pleuropulmonary Manifestations of Hepatic Amebiasis*

Symptom	*Patients* No.	*Patients* %
Right upper quadrant pain	15	50
Other abdominal pain	10	33
Other complaints		17
Right shoulder pain	1	
Cough	1	
Fever	1	
Nausea and vomiting	2	

TABLE 3.—*Clinical Findings in 30 Patients With Pleuropulmonary Manifestations of Hepatic Amebiasis*

Symptoms	*Patients* No.	*Patients* (%)	*Signs*	*Patients* No.	*Patients* (%)
Fever	29	(97)	Elevated temperature	27	(90)
Abdominal pain	25	(83)	Abdominal tenderness	22	(73)
Sweats	18	(60)	Hepatomegaly	14	(47)
Diarrhea	14	(47)			
Pleuritic pain	12	(40)	Decreased breath sounds	11	(37)
Shoulder pain	7	(23)	Chest dullness	5	(17)
Cough	7	(23)	Crackles	4	(13)
Dyspnea	2	(7)	Consolidation	2	(7)
Sputum production	1	(3)	Pleural rub	1	(3)

TABLE 4.—*Admission Chest Roentgenograms in 30 Patients With Pleuropulmonary Manifestations of Hepatic Amebiasis*

Chest Roentgenogram Findings	*Patients* No.	*Patients* %
Normal	14	46
Abnormal	16	53
Right pleural effusion	9	30
High right hemidiaphragm	8	27
Right basilar atelectasis	4	13
Multiple abnormalities	4	13

acid-fast stains and cultures for acid-fast bacilli. In addition, smears of the fluid were negative for parasites.

All patients in this series responded to treatment regimens that included metronidazole (Flagyl). During the study period at our institution, there were no deaths from amebic liver abscess.

Discussion

The expectoration of anchovy-paste-like material by a patient who has recently arrived from a third-world nation is virtually pathognomonic of a hepatopulmonary fistula from an amebic liver abscess.[8-10] Most clinicians would make the correct diagnosis in a patient presenting in this manner. Unfortunately for physicians, the percentage of patients presenting with hepatic amebiasis who cough up this reddish-brown material is small.[6] Thus, as pointed out by Patterson and Schoppe, "one must rely on a high degree of clinical suspicion and the recognition of a well-described clinical syndrome" to correctly diagnose most cases of the disorder.[1]

Patients with amebic liver abscess generally present with a variety of symptoms that focus attention to the right upper quadrant. Two patients in our series were initially admitted to the surgical service with the diagnosis of acute abdomen. Often such patients also have signs and symptoms referable to the chest, and sometimes these pulmonary findings dominate the clinical picture. In our series, two patients (7%) presented with pulmonary symptoms as their chief complaint, and one was initially misdiagnosed as having pneumonia. Kubitschek and co-workers recently published a series in which seven patients were admitted to the hospital with predominantly pulmonary symptoms and were found to have an amebic liver abscess.[9] Moreover, even when the abdominal symptoms were foremost, most (60%) of our patients presented with pulmonary symptoms and almost half (47%) had pulmonary signs. These findings are similar to those of Adams and MacLeod, who reviewed 146 cases of hepatic amebiasis in South Africa.[2] They found that a substantial number of patients presented with right-sided chest pain (28%), cough (11%), right shoulder pain (9%), shortness of breath (4%), and "signs" at the right lung base (47%).

Figure 1.—A chest roentgenogram of a patient with amebic liver abscess shows a right pleural effusion, elevated right hemidiaphragm, and right basilar atelectasis.

Thoracic complications of amebiasis virtually always occur in the presence of a hepatic abscess. When pleuropulmonary involvement occurs, a variety of manifestations may be found. One complication, seen in six of our patients (20%), occurs when an enlarged liver causes elevation of the right diaphragm with subsequent right basilar atelectasis. Infection below the diaphragm may also cause the formation of a pleural effusion.[9] In our series, 12 patients (40%) had radiographic evidence of a pleural effusion. In only three was fluid obtained for examination: bloody, purulent fluid was described in one and the other two had serous and serosanguineous fluid. All three fluids were stain- and culture-negative, consistent with the noninfectious, reactive nature of most pleural effusions due to hepatic amebiasis.[3,9] Amebic empyema formation is a separate complication and is caused by the rupture of a hepatic abscess into the pleural space. An amebic liver abscess may also rupture into the lung parenchyma itself, leading to pulmonary abscess formation. An abscess may rupture into an airway, causing a hepatopleurobronchial fistula to form. None of the patients in our series had either of these complications, but in one patient who was clinically responding to treatment, hemoptysis developed that may have been due to rupture of an amebic liver abscess into a bronchus. The rupture of an amebic liver abscess into the pericardial space, a complication associated with left hepatic lobe abscesses and a high mortality,[3] was not seen in any of our patients.

All 30 patients in our series responded to treatment with amebicidal drugs (a drug regimen including metronidazole was used in all the cases reported). Seven patients underwent percutaneous aspiration of their liver abscesses for diagnostic purposes. Three indications for doing an aspiration of an amebic liver abscess are uncertainty of the diagnosis, a failure to respond to adequate noninvasive treatment, and "impending rupture."[8]

The indications for the drainage of pleural effusions due to amebiasis are similar to those for aspiration of a hepatic abscess. A thoracentesis is indicated if the diagnosis is in doubt or if a patient fails to respond to adequate amebicidal therapy. Some authors, though, advocate sampling of all pleural fluid to confirm the diagnosis and to rule out secondary bacterial infections.[9] Three patients in our series underwent diagnostic thoracentesis, and of these, one had chest-tube drainage for symptomatic relief of a large right-sided pleural effusion. All 12 patients with effusions responded to metronidazole (Flagyl) therapy with defervescence and a resolution of their pleural effusions. We recommend initial treatment of hepatic amebiasis-associated pleural effusions with a trial of metronidazole, 750 mg orally three times a day for 10 days. To eradicate intestinal amebae, the addition of iodoquinol, 650 mg orally three times a day for 20 days, should also be considered. Metronidazole has been shown to penetrate the pleural space and should be effective except in complicated cases.[11] The drainage of fluids should be reserved for patients who do not respond promptly to amebicidal therapy or who are symptomatic because of a large effusion.

In summary, we describe the pleuropulmonary manifestations of amebic liver abscess. Because the disease is potentially fatal and prompt treatment is generally successful, clinicians must consider this diagnosis in patients from endemic areas who present with symptoms and signs refer-

able to the lung bases. These symptoms and signs are common in amebic liver abscess and in some patients may be the presenting features. Specific diagnostic techniques or treatment modalities, such as chest-tube drainage, are not often necessary as the pulmonary features resolve with therapy directed at the amebiasis.

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THE OPERATORS' ROOM

The helix of power runs still but deep
This inner-sanctum's secrets keep
With only the eyes exposed to read
Continual mayhem, but no orbs weep
The Bard-Parker drops, for guests to bleed
But words cut a longer and deeper need

Both regimented, but totally loose
A leer, bump, squeeze or goose
Pinches, hugs, conglomerate jokes
All secret and sacred—no tellers or noose
Heavy drinking—but just Diet Cokes
Intimacy's dual is both real and hoax

Nudes, life, terror and tension
Bodies touching with honorable mention
Complex professional and social grating
Parties with anatomical dimension
Emperors with their ladies in waiting
Sex, power, and money mating

All priestly nurses in billowy gowns
This Holy of Holies is for most out of bounds
Spouses may call but are abruptly evaded
Don't cross the red line without your crowns
But here's why the O.R.'s never raided
Advances are not reported, but graded.

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Barriers to Prescribing the Copper T 380A Intrauterine Device by Physicians

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From a questionnaire sent to all obstetricians and gynecologists and all family and general practitioners in San Diego County, California, regarding the Copper T 380A intrauterine device, substantial barriers to prescribing it were identified. Of all physicians responding, 40% reported that they were not recommending the Copper T 380A to anyone, the single most common reason given being concern about medical liability. A lack of knowledge about the new device, a lack of intrauterine device insertion skills, and certain medical practice settings were also important barriers to prescribing it. The new intrauterine device is considered in the context of innovation-diffusion theory. Substantial amounts of education and training and improvement in the medical-legal climate are needed before current barriers to prescribing the new device are removed.

(Kooiker CH, Scutchfield FD: Barriers to prescribing the Copper T 380A intrauterine device by physicians. West J Med 1990 Sep; 153:279-282)

The World Health Organization has stated that the new-generation copper-containing intrauterine devices (IUDs) are comparable in safety and efficacy to oral contraceptives.[1] Unfortunately, negative publicity associated with medical-legal issues caused major United States manufacturers to discontinue the domestic sale of IUDs in 1986, leaving only the intrauterine progesterone contraceptive device, Progestasert, on the US market. This discontinuation of sales of copper-containing IUDs has caused a decline in the number of women using IUDs from 2.7 million in 1973 to an estimated 1.4 million in 1985.[2]

In late spring of 1988 a new IUD, the Copper T 380A, became available in the United States under the trade name of ParaGard (GynoPharma, Somerville, NJ). This T-shaped IUD has the improved clinical characteristics of a failure rate of less than 1 pregnancy per 100 women-years-of-use[3,4] and a longer use interval of four years.[5] There has been concern, however, that nonmedical barriers to the prescribing of this new device by physicians may exist.

To identify possible barriers to prescribing the Copper T 380A, in the fall of 1988 we surveyed a sampling of physicians to examine their knowledge, attitudes, and practices regarding this new IUD.

Methods

We obtained a mailing list from the county medical society of all obstetricians and gynecologists and all family practitioners and general practitioners with an office address in San Diego County, California. The list contained 245 obstetricians and gynecologists and 651 family and general practitioners, for a total sample size of 896 physicians. They were given three opportunities to respond to a pretested mail questionnaire. Of the 896 physicians, 25 were excluded from the sample because we learned that they were retired, living out of the county, or deceased, leaving 871 possible respondents. Of these, we had a total of 473 responses for a 54% overall response rate.

Of our respondents, 78 or 16% said they did not provide family-planning services and, therefore, were excluded from further analysis. Thus, the final sample was 395, including 133 obstetricians and gynecologists and 262 family and general practitioners. Of these, 80% were in private practice, 13% were in health maintenance organizations (HMOs), 4% were in nonprofit health systems, and 3% were in governmental health systems.

To check for response bias, we made a telephone survey of a 10% sample of our nonrespondents. Of the 42 persons called, 4 had formally retired and 9 no longer had a business phone listing. Using a two-sample test for binomial proportions to compare our respondents and nonrespondents, we found no significant differences ($P > .05$) between the two groups in age, sex, practice setting, specialty, in providing family-planning services, or in the proportion who recommended the new IUD.

We asked physicians for their "current approach to the Copper T 380A IUD," giving four options to choose from:

- Recommend to no one.
- Recommend to selected patients but refer them to other physicians for insertion.
- Recommend to selected patients and plan to insert once the Copper T 380A is received.
- Recommend to selected patients and am currently inserting.

We used the χ^2 test to examine the association between the dependent variable, "current approach to the use of the IUD" and various hypothesized independent variables. To compare the probabilities of various groups *not* recommending the new IUD, odds ratios were calculated (Tables 1, 2, and 3). Confidence intervals (CIs) of 95% were constructed using the Taylor's series method.

Finally, we examined the reasons given by the 152 physicians who did not recommend the IUD to any of their patients.

Results

Only 17% of the respondents were currently inserting IUDs; 23% referred patients elsewhere for insertion, 21% planned to insert the device once they received it, but a full 40% did not recommend the IUD to anyone.

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ABBREVIATIONS USED IN TEXT

CI = confidence interval
HMO = health maintenance organization
IUD = intrauterine device

Family and general practitioners were much more reluctant to recommend or insert the new IUD than were obstetricians and gynecologists (Figure 1). Of the family and general practitioners, 47% did not recommend the new IUD as compared with 26% of the obstetricians and gynecologists. Thus, family and general practitioners were 2.6 times more likely not to recommend the new IUD than were their colleagues in obstetrics and gynecology (95% CI, 1.6 to 4.2). Even among those recommending the new IUD, most referred patients elsewhere for insertion. In fact, only 22% of family and general practitioners were inserting or planning to insert the new IUD compared with 65% of obstetricians and gynecologists.

Obstetrician-gynecologists and family and general practitioners employed by HMOs were particularly reluctant to get involved in prescribing and inserting the new IUD; 49% did not recommend it to anyone; they were 3.4 times more likely to not recommend the IUD than were their colleagues working for nonprofit or governmental institutions (Table 2). Furthermore, none of the HMO physicians were currently inserting the new IUD. Physicians working for nonprofit or governmental facilities were more receptive to the IUD, with 58% either already inserting it or planning to insert it. The number of physicians in private practice prescribing and inserting the new IUD was midway between these two groups.

Most physicians were not correctly informed about the improved clinical characteristics of the new IUD. We asked two questions to assess physicians' knowledge of the new IUD. When asked the pregnancy failure rate in women 25 years of age or older, only 27% of the physicians answered correctly. The percentage of correct responses did not differ significantly between the obstetrician-gynecologist and family-general practitioner groups. Next we asked how often the Copper T 380A should be replaced. Answers to this question differed between the two specialty groups: 55% of obstetricians and gynecologists responded correctly, as opposed to only 11% of family and general practitioners.

A low IUD knowledge score was strongly associated with a negative attitude toward the new IUD and a reluctance to recommend it (Table 2). Those who answered both questions incorrectly were 14.8 times more likely not to recommend the new IUD than were those who answered at least one correctly. Of the 35 physicians who knew the correct answers to both questions, only 1 (3%) said that he did not recommend the IUD, and 60% reported that they were already inserting it.

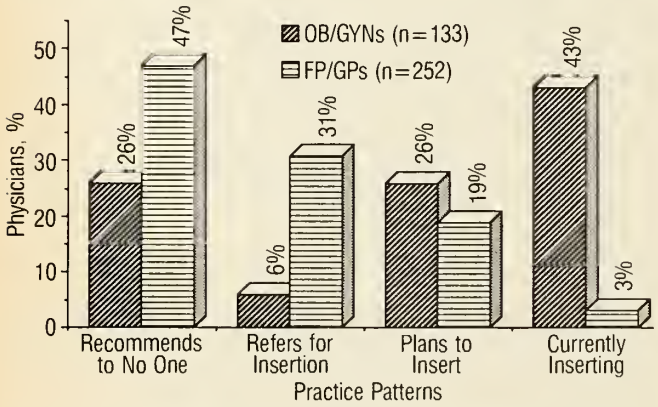

Figure 1.—The graph shows practice patterns of obstetrician-gynecologists (OB/GYNs) and family and general practitioners (FP/GPs) in prescribing the Copper T 380A. (The percentages for OB/GYNs add up to more than 100% due to rounding of numbers.)

Of the family and general practitioners, only 35%—as compared with 5% of the obstetricians and gynecologists—said that they had inserted 14 or fewer IUDs of all types. (The World Health Organization suggests that trainees need to do at least 10 to 15 IUD insertions under supervision before they have the skill and self-confidence to do it alone.[1]) None of these physicians with minimal experience in placing IUDs were currently inserting the Copper T 380A. Moreover, most of these physicians were not recommending the new IUD to any patients (Table 3).

Reasons Some Physicians Never Recommend the Copper T 380A

Of the 152 physicians who did not recommend the new IUD to anyone, only 136 indicated why. The most frequent reason was concern about medical liability (54 respondents, or 40%). Medical safety was the second most common concern of 41 (30%). A concern that the IUD may act as an abortifacient was the primary reason for 13 (10%).

TABLE 1.—*Rates and Odds Ratios of Physicians Not Recommending the Copper T 380A Intrauterine Device (IUD) by Medical Practice Setting (N=365)*

Practice Setting	*Rate**	*Odds Ratio†*	*95% CI*
Nonprofit or governmental	22	1.0	Referent
Private practice	39	2.2	0.8 to 6.3
Health maintenance organization	49	3.4	1.04 to 11.3

CI = confidence interval

*Per 100 physicians.
†Based on an index rate of 22 per 100 physicians working in nonprofit or governmental health facilities *not* recommending the new IUD to anyone.

TABLE 2.—*Rates and Odds Ratios of Physicians Not Recommending the Copper T 380A by Physician Knowledge About the New Intrauterine Device (IUD) (N=307)*

*Physician's Knowledge**	*Rate†*	*Odds Ratio‡*	95% CI
2 of 2	3	1.0	Referent
1 of 2	30	14.6	2.1 to 79.7
0 of 2	42	24.8	3.5 to 111.5

CI = confidence interval

*Number of correct reponses to 2 questions (efficacy and duration of use) about the Copper T 380A.
†Per 100 physicians.
‡Based on an index rate of 3 per 100 physicians with a perfect knowledge score *not* recommending the new IUD.

TABLE 3.—*Rates and Odds Ratios of Physicians Not Recommending the Copper T 380A Intrauterine Device (IUD) by Post Experience With Insertion of IUDs (N=383)*

Number of Insertions	*Rate**	*Odds Ratio†*	*95% CI*
>25	31	1.0	Referent
15-25	51	2.4	1.1 to 5.0
1-14	46	1.9	0.99 to 2.7
None	69	5.0	2.3 to 10.7

CI = confidence interval

*Per 100 physicians.
†Based on an index rate of 31 per 100 physicians who have inserted more than 25 IUDs of any type *not* recommending the new IUD to anyone.

Only 4 physicians (3%) answered that their major concern was that the new IUD was too expensive. Most of the remaining reasons related to a lack of information about the IUD.

Discussion

The most striking finding of this study is that 40% of the respondents did not recommend the Copper T 380A to anyone. Of further importance is that 23% more responded that they recommended the new IUD but referred their patients to someone else to insert it. This referral may well represent a barrier to women using the IUD because it means additional costs, inconvenience, and delays in getting birth control.

The introduction of the Copper T 380A can be viewed as a contraceptive innovation in that it is perceived by at least part of the medical community as new. Kotler points out that innovations are assimilated into a social system over time through a diffusion and adoption process.[6] Diffusion is the long-term process of the spread of a new idea from its source of invention all the way to its ultimate users or adopters. The adoption process is more circumscribed and focuses on the mental processes that persons pass through from the time they hear of an innovation until they become regular users.

Space does not allow for a full description of innovation-diffusion theory, but it may be helpful to summarize its basic tenets:

- People differ greatly in their willingness to try new products.
- Each person goes through a series of stages in the adoption process, including an initial awareness of the existence of the innovation, an interest in it and attempts to seek additional information, evaluation, individual trial on a small scale, and adoption.
- Opinion leaders play a large role in the adoption of new products.
- The nature of the innovation itself affects the rate of adoption.[6]

When the Copper T 380A IUD is considered in the context of innovation-diffusion theory, the results of our study take on a new perspective. This study suggests that we are in the midst of a technologic diffusion process as a new copper IUD is released into the medical system after a relative IUD hiatus of more than two years. This cross-sectional survey is like a snapshot of physician practices during the fall of 1988, about six months after distribution of the Copper T 380A began. At the time of the snapshot, 38% of the physicians who would be most likely to adopt this new contraceptive innovation—obstetrician-gynecologists and family and general practitioners—had progressed to the point that they planned to insert it, but only 17% currently had the Copper T 380A in stock in their offices.

Family and general practitioners and obstetrician-gynecologists differ in their approach to the Copper T 380A. Physicians in family and general practice were less knowledgeable about the improved features of the Copper T 380A. They had considerably less experience inserting IUDs, were less inclined to recommend the Copper T 380A, and were much less likely to be inserting it.

Physicians practicing in HMOs seem to be the least willing to recommend the Copper T 380A, and public-governmental sector physicians appear to be the most receptive to recommending it. Unsolicited written comments on the questionnaire from several HMO physicians showed concern within their organizations about the manufacturer's ability to withstand a possible barrage of legal suits and concern that HMOs might then become a "deep-pocket" target for liability suits.

Most physicians lacked current knowledge about the Copper T 380A. Nearly half (47%) answered that the pregnancy failure rate of the Copper T 380A was 3 to 5 pregnancies per 100 women-years-of-use, and more than a third (38%) answered that 3 was the maximum number of years the Copper T 380A is approved for use. These answers are correct for the second-generation copper IUDs such as the Copper 7 (G.D. Searle Co, Skokie, Ill). This lack of knowledge suggests that many physicians have not assimilated the new (and more favorable) information about the third-generation Copper T 380A. Because poor knowledge scores were associated with a reluctance to recommend the IUD, continuing medical education on this subject is a worthy objective.

The data suggest that a substantial minority of physicians lack experience in inserting IUDs and that these physicians are also particularly reluctant to recommend the new IUD even when they could refer patients to someone else for insertion. It would seem advisable to develop training programs for these physicians.

Physicians' Concern About Liability as a Barrier

Of special concern is the fact that 54 of the 136 physicians (40%) who did not recommend the Copper T 380A to anyone said the main reason was concern about medical liability. Thus, health decisions are being made on the basis of the fear of being sued and not on the basis of the medical benefits and risks.

Before about 1985, the increased incidence in pelvic inflammatory disease seen in IUD users was ascribed to the device itself. This may be true for the Dalkon Shield. Recent epidemiologic evidence suggests, however, that the increased incidence in pelvic inflammatory disease associated with copper-bearing IUDs is more appropriately ascribed to the previous practice of inserting IUDs without screening for behavioral risk factors for sexually transmitted diseases.[7-11] These same recent studies support the evidence that the copper-bearing IUDs pose a low risk of pelvic inflammatory disease or infertility to women whose sexual life-style—stable, mutually monogamous sexual relationships—puts them at low risk for sexually transmitted diseases. Responses to our survey imply that physicians do understand that the Copper T 380A represents a very small medical risk to selected patients, but they refuse to recommend it.

From a legal perspective, all prescription products are considered "unavoidably unsafe," which means that they cannot be made totally safe for all users.[12] Thus, the law directs that such products are reasonably safe if accompanied by appropriate warnings from physicians. In the case of IUDs and oral contraceptives, federal law goes further, requiring manufacturers to inform patients directly about the risks and benefits of their products. For the Copper T 380A, GynoPharma has produced an information brochure that functions as a detailed informed consent booklet.[13]

Limitations of Our Study

Although the questionnaire was pretested on medical practitioners, the internal validity of the survey instrument has not been repeatedly checked. For example, we learned that there is a certain ambiguity in the word "recommend." Several physicians commented that they never "recommend" any IUD, but that if other methods are contraindicated or unacceptable, they will prescribe an IUD as a second-choice method. Also, the study surveyed physicians

in only one locale, which makes generalizations regarding physicians throughout the United States questionable. Finally, nonphysicians such as nurse practitioners and midwives recommend birth control methods. Studies of their knowledge and practices regarding the Copper T 380A IUD would be important.

Summary

Our study suggests that there are important attitudinal, informational, and experiential barriers to the prescribing of the Copper T 380A IUD. An improvement in the medical-legal climate and substantial education and training are needed before current barriers will be removed. If this can be done, then women will be able to make contraceptive choices based on appropriate medical criteria, not extraneous barriers from medical providers.

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Does Paramedic-Base Hospital Contact Result in Beneficial Deviations From Standard Prehospital Protocols?

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Presented in part at the University Association for Emergency Medicine, Minneapolis, Minnesota, May 1989.

We reviewed written and audio records of paramedic-base hospital radio contact to determine whether care differed from that suggested in standard prehospital care protocols. Records of all 659 contacts for seizure, syncope, abdominal pain, or altered mental state during 1987 (28.4% of all contacts) were scored for the use of standard therapies (such as intravenous access, oxygen, naloxone hydrochloride) and unanticipated therapies (intubation, nitroglycerin). Cases that involved unanticipated treatments were reviewed to determine whether they could have been prospectively identified by simple clinical findings. Standard therapies were used in the majority of patients. Unanticipated therapies were administered to 13 patients, all of whom had abnormal vital signs, diaphoresis, respiratory distress, or a second prominent symptom. Data suggest that protocols could replace radio contact for most patients and that the few who might benefit from radio contact can be easily identified. A 90% reduction in radio contacts in Los Angeles county could save $3 million each year.

(Hoffman JR, Luo J, Schriger DL, Silver L, et al: Does paramedic-base hospital contact result in beneficial deviations from standard prehospital protocols? West J Med 1990 Sep; 153:283-287)

In the past two decades there has been a tremendous expansion in the prehospital care capabilities of many communities throughout the United States. While paramedic programs provide substantial benefit in terms of patient care, the cost associated with these systems is large. This fact is in part responsible for the reliance in many areas on less costly, less sophisticated emergency medical systems, employing only basic emergency medical technicians.

Much of the cost of advanced life-support systems relates to the training and payment of the providers, but ancillary costs, including telemetry equipment, radio communication facilities, and on-line medical control personnel, add significantly to the total expenditures of such programs. Several previous studies have questioned the cost-effectiveness of some of these elements. Indeed, a number of emergency medical services systems now allow paramedics to treat patients on the basis of standardized protocols, and excellent results using such an approach have been reported.[1,2]

In Los Angeles paramedics are authorized to provide medical care essentially only under the direct supervision of certified base-hospital physicians or certified mobile intensive care nurses; rare exceptions in special circumstances do occur. Paramedics in the field communicate with these in-hospital personnel through radio communication devices, often using cardiac telemetry as well. With 34 base hospitals supervising 274 paramedic units, the cost involved in merely maintaining these base-hospital facilities and on-line personnel has been estimated at more than $7 million each year.[3]

For many common prehospital chief complaints reported to our base hospital by field paramedics, treatments ordered almost never vary and generally follow simple protocols. The prehospital management of patients with these chief complaints would be easily amenable to an algorithm-directed system, which would bypass the need for direct hospital communication. This in turn would dramatically diminish the number of radio calls paramedics would have to make, thus allowing for the consolidation of base stations and ultimately translating into substantial cost savings.

We chose four common (28.4% of all our paramedic calls in 1987) prehospital chief complaints (abdominal pain, history of a syncopal episode, history of a seizure, and altered mental state) for which we felt almost all patients within each group are generally treated similarly, and we abstracted simple locally published algorithms (Figure 1) to reflect the treatment steps we think are routinely ordered.[4] We hypothesized that virtually all patients with these chief complaints are managed at our base hospital in concordance with such algorithms (which also reflect standard published guidelines for the prehospital treatment of these conditions). If this is true, it would provide a strong rationale for allowing paramedics to treat future patients, at least with these chief complaints, precisely according to the algorithms, without first having to establish radio contact with hospital personnel.

Materials and Methods

UCLA Hospital is a 711-bed acute care university teaching hospital. The UCLA Emergency Medicine Center provides care for 44,000 patients each year and also acts as the paramedic base hospital for seven local paramedic units. Paramedic radio calls are handled primarily by certified mobile intensive care nurses working in the Emergency Medicine Center and by junior residents in the UCLA Emergency Medicine Residency Program who have been trained and certified as base-station physicians according to Los Angeles County guidelines. Backup consultation is available as needed from attending physicians and senior residents in emergency medicine.

The UCLA paramedic base hospital directs prehospital care given by paramedics to approximately 2,400 patients

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each year, in each case communicating directly with paramedics on the scene through a two-way radio; cardiac telemetry is also available. Paramedics may administer oxygen and obtain intravenous access before establishing radio contact; in rare and special circumstances—cardiac arrest, inability to establish radio contact—certain other activities may be begun according to preexisting protocols. On routine calls other "advanced life-support" interventions (such as administering large quantities of intravenous fluids, giving medications, electrical cardioversion, endotracheal intubation) are accomplished only on the direct order of base-hospital medical control personnel.

We reviewed the medical records and the tape-recorded radio contacts between field paramedics and UCLA base-hospital personnel for all patients with one of four specific chief complaints whose care was directed by the UCLA paramedic base hospital during the calendar year 1987. The four chief disorders were abdominal pain, history of a recent seizure, history of a syncopal episode, and altered mental state. There were no exclusion criteria.

We compared treatment orders given for patients in each of these groups with treatment algorithms constructed in accordance with widely disseminated guidelines for the prehospital care of patients[4] in an attempt to determine whether variations in treatment indeed occurred for patients within any of these treatment groups. We also evaluated other clinical criteria, such as vital signs at presentation, to determine the basis for those variations that did occur. Finally, we attempted to evaluate whether a deviation from protocol was likely to have significantly affected the outcome of individual patients.

Treatment Algorithms

Abdominal Pain

ABCs; oxygen, 4-6 liters/min; IV normal saline solution
Cardiac monitor (see arrhythmia algorithm if any arrhythmias)
If adequate perfusion (with systolic BP > 90 mm of mercury),
  keep IV open; transport
If hypoperfusion,
  Inflate MAST; 500-ml IV fluid bolus; transport; start 2nd IV en route

Syncope

ABCs; oxygen, 4-6 liters/min; IV normal saline solution
Cardiac monitor (see arrhythmia algorithm if any arrhythmias)
If suspected trauma,
  backboard, cervical collar, sandbags
If normotensive,
  keep IV open; transport
If hypotensive (BP < 90 mm of mercury),
  consider inflating MAST; 500-ml IV fluid bolus; consider giving dopamine; transport; start 2nd IV en route
If recurrent loss or alteration of consciousness,
  administer naloxone HCl, 0.8 mg IV; dextrose, 25 grams IV (glucagon 1 mg IM if no IV); consider giving thiamine
If inadequate respirations and no gag reflex,
  consider effective oxygen administration or endotracheal intubation
Transport

Altered Mental State

ABCs; oxygen, 4-6 liters/min; IV normal saline solution
Cardiac monitor (see arrhythmia algorithm if any arrhythmias)
Administer naloxone HCl, 0.8 mg IV; dextrose, 25 grams IV (glucagon, 1 mg IM if no IV); consider giving thiamine
If suspected trauma,
  backboard, cervical collar, sandbags
If normotensive,
  keep IV open; transport
If hypotensive (BP < 90 mm of mercury),
  consider inflating MAST; 500-ml IV fluid bolus; consider giving dopamine; transport; start 2nd IV en route
If inadequate respirations and no gag reflex,
  consider effective oxygen administration or endotracheal intubation
Transport

Seizures

ABCs; oxygen, 4-6 liters/min
If normal level of consciousness,
  IV normal saline solution; draw blood specimens while starting IV (this may be unnecessary in patients with known epilepsy)
If altered level of consciousness,
  IV normal saline solution; draw blood specimens while starting IV; administer naloxone HCl, 0.8 mg IV; dextrose, 25 grams IV (consider giving glucagon, 1 mg IM if no IV); consider giving thiamine
If suspected trauma,
  backboard, cervical collar, sandbags
If recurrent seizure activity,
  maintain airway and have suction available
  administer diazepam (Valium), 5-20 mg, slow IV titrate to effect; dose in children, 0.2 mg/kg to 10 mg maximum
  naloxone HCl, 0.8 mg IV; dextrose, 25 grams IV (consider giving glucagon, 1 mg IM if no IV); consider giving thiamine
If inadequate respirations and no gag reflex,
  consider effective oxygen administration or endotracheal intubation
Transport

Figure 1.—Treatment algorithms used at the UCLA Emergency Medicine Center are shown for the four most common complaints requiring emergency medical services. ABCs = airway, breathing, and circulation [examination]; BP = blood pressure; HCl = hydrochloride; IM = intramuscular; IV = intravenous; MAST = military antishock trousers

Results

Included in this series are 659 patients; they represent 28.4% of the 2,316 patients whose prehospital care was supervised by the UCLA base hospital during the calendar year 1987. Of these, 101 had a chief complaint of abdominal pain, 261 had a syncopal episode, 207 had an altered mental state, and 90 had been witnessed to have a seizure. Demographic characteristics of these patients are listed in Table 1, and vital signs are listed in Table 2. The large majority of patients had normal vital signs, but 2.6% of patients had bradycardia, and 16.4% had tachycardia. Similarly, hypotension (systolic blood pressure less than 90 mm of mercury) occurred in 7.0% and hypertension (systolic blood pressure greater than 160 mm of mercury) in 14.1%. A small number of patients (3.2%) had bradypnea (respirations 12 or fewer per minute), and 21.1% had tachypnea (respirations more than 20).

Standard therapies, such as supplemental oxygen, intravenous access, cervical spine precautions for patients with known or possible trauma, and medications for altered mental state (hypertonic glucose solution, naloxone hydrochloride, or thiamine) were frequently used. Well over 90% of patients in each of the four groups received intravenous (IV) access; only 43 patients in all (6.5%) did not have an IV line placed (Table 3). On the other hand, only 29 patients (4.4%) had more than one IV line; this was particularly prevalent in patients with abdominal pain, where 11.9% had two or more IV lines. Almost 21% of patients with abdominal pain and 13% of the entire group had fluid boluses of at least 200 ml while in the field. The majority (56 of

TABLE 1.—*Demagraphic Characteristics of Study Patients (n = 659), by Chief Complaint*

Characteristic	*Abdominal Pain*	*Syncope*	*Altered Mental State*	*Seizure*
Patients, No.	101	261	207	90
Mean age, yr*	49.8 ± 21.6	67.0 ± 19.0	57.2 ± 23.9	39.7 ± 18.9
Male sex, No. (%)	36(35.6)	115(44.1)	109(52.6)	57(63.3)

*Value given as mean ± standard error of the mean.

TABLE 2.—*Vital Signs in 659 Prehospital Patients, by Chief Complaint*

Vital Sign		Patients: Abdominal Pain, No. (%)	Syncope, No. (%)	Altered Mental State, No. (%)	Seizure, No. (%)	Total No. (%)
Heart rate, beats/min	< 60	0 (0)	9 (3.4)	8 (3.9)	0 (0)	17 (2.6)
	60-100	86 (85.1)	236 (90.4)	154 (74.4)	58 (64.4)	534 (81.0)
	>100	15 (14.8)	16 (6.1)	45 (21.7)	32 (35.6)	108 (16.4)
Systolic blood pressure, mm of mercury	< 90	8 (7.9)	22 (8.4)	15 (7.2)	1 (1.1)	46 (7.0)
	90-160	84 (83.2)	211 (80.8)	156 (75.4)	69 (76.7)	520 (78.9)
	>160	9 (8.9)	28 (10.7)	36 (17.4)	20 (2.2)	93 (14.1)
Respiratory rate/min	<13	1 (1.0)	3 (1.1)	10 (4.8)	7 (7.8)	21 (3.2)
	13-20	77 (76.2)	223 (85.4)	133 (64.2)	66 (73.3)	499 (75.7)
	>20	23 (22.8)	35 (13.4)	64 (30.9)	17 (18.9)	139 (21.1)

TABLE 3.—*Intravenous (IV) Use in 659 Prehospital Patients*

Chief Complaint	Patients, No.	IV Line, No. (%)	> 1 IV Line, No. (%)	Fluid Challenge, No. (%)
Abdominal pain	101	95 (94.0)	12 (11.9)	21 (20.8)
Syncope	261	241 (92.3)	4 (1.5)	43 (16.5)
Altered mental state	207	198 (95.7)	12 (5.8)	19 (9.2)
Seizure	90	82 (91.1)	1 (1.1)	3 (3.3)
Total	659	616 (93.5)	29 (4.4)	86 (13.0)

TABLE 4.—*Presence of Trauma History, Altered Mental State, or Both, in Patients Receiving Trauma Precautions*

Chief Complaint	Patients, No.	Trauma History, No. (%)	Altered Mental State, No. (%)	Neither, No. (%)
Abdominal pain	10	2 (20)	0 (0)	8 (80)
Syncope	11	1 (9)	6 (55)	4 (35)
Altered mental state	25	8 (32)	17 (68)	0 (0)
Seizure	10	1 (10)	7 (70)	2 (20)
Total	56	12 (21)	30 (54)	14 (25)

TABLE 5.—*Use of Empiric Glucose Solution, Naloxone Hydrochloride, or Thiamine in 659 Prehospital Patients*

Protocol Used	Chief Complaint, No. of Patients: Abdominal Pain	Syncope	Altered Mental State	Seizure
Yes	0	35	176	54
No	101	226	31	36

TABLE 6.—*Unusual Interventions in 659 Prehospital Patients*

Intervention	Patients, No.	Indication (Patients)
Endotracheal intubation	1	Respiratory depression, altered mental state
Lidocaine	26	Ectopic beats, usually in patients with seizure (21); unclear (5)
Sublingual nitroglycerin	5	Elevated BP, rales, diaphoresis (1); elevated BP (1); diaphoresis, rales, abdominal pain (2); tachycardia, abdominal pain (1)
Morphine sulfate	1	Abdominal pain, rales, diaphoresis
Atropine sulfate	4	Bradycardia
Aminophylline	1	"History of asthma"
Furosemide	2	Diaphoresis, rales (1); unclear (1)
Dopamine	2	Hypotension

BP = blood pressure

86, or 65.1%) of patients receiving such therapy had either tachycardia, hypotension, or both; conversely, only 39 other patients with these same abnormalities in vital signs did not receive a similar fluid challenge.

Most patients (91%) received supplemental oxygen, including all patients with abnormal respiratory rates. Trauma precautions (backboard or hard cervical collar) were carried out in a small number of patients (56, or 8.5%), including not only 12 patients (21%) with a documented history or physical evidence of trauma at the time of the call but, even more common, patients with an abnormal mental state at the scene of the medical emergency (30 of 56, or 54%); 14 patients (25%) had these precautions ordered despite no evidence of either of these factors (Table 4). A subsequent review did not reveal any of these last patients to have benefited from such precautions, which were routinely removed after the patient's arrival in an emergency department.

Standard protocol medications for altered mental state (hypertonic glucose solution, naloxone, thiamine, or a combination of all three) were used in the large majority (176 of 207, or 85.0%) of patients with this chief complaint and in 35 patients (39%) having had a seizure. They were rarely used in patients with syncope (5.7%) and not used in patients with abdominal pain (Table 5). It is not clear why such medications were omitted in any of the patients with a chief complaint of an altered mental state, although some of these patients may have had a return to normal to some degree at the time of the base-hospital contact. None of the 15 postsyncopal patients receiving these medications had current changes in their mental state, and none responded in any way. Of the 35 postseizure patients receiving these medications, most (85, or 94%) had postictal confusion at the time of the call. Three had equivocal responses to this treatment, which on review appeared in each patient to reflect the natural progression of awakening following the seizure, rather than any medication effect.

Other interventions, including the use of antiarrhythmic therapy (lidocaine), analgesic medication, other medications, and endotracheal intubation, were used rarely (Table 6). The one patient requiring intubation had an altered mental state and a respiratory rate of 8 per minute. In all, 26 received intravenous lidocaine, including 17 patients with a history of a syncopal episode. Of the 26 patients, 21 had ectopic beats on cardiac monitor strips; the indication for using lidocaine in the other patients is unclear.

Twelve patients (1.8%) received 14 other medications. Two patients with syncope received sublingual nitrates for elevated blood pressure, associated in one case with diaphoresis, pulmonary rales, and tachycardia. One patient with syncope, two patients with altered mental state, and

one patient with abdominal pain received atropine sulfate for bradycardia. Three patients with abdominal pain received nitrates, in one patient along with parenteral morphine sulfate and furosemide; two of these patients had gross diaphoresis and had rales on lung examination, while the other had tachycardia. One other patient with altered mental state also received furosemide, for uncertain reasons. Two patients with altered mental state and pronounced hypotension received dopamine infusions.

One patient with an altered mental state and a history of asthma received aminophylline, although there was no indication at the scene or subsequently that the acute event had any relation to ventilatory problems.

When the individual groups are looked at separately, the results are generally similar. Most patients with an altered mental state (144 of 207, or 70%) received all four elements of the protocol (IV line, supplemental oxygen, glucose solution, and naloxone), and 205 (99%) received at least one of the four; few other modalities were used. Of the 90 patients with a previous seizure, 34 (38%) received all of these interventions, while 81 (90%) received at least an IV line and supplemental oxygen. The large majority (196 of 261, or 75%) of patients with syncope also received an IV line and oxygen therapy, with several others receiving other generally innocuous therapies. Similarly, therapy for abdominal pain consisted almost uniformly (85 of 101, or 84%) of an IV line and oxygen; 11 patients receiving more than one IV line had tachycardia or hypotension or were young women with lower abdominal pain. Other therapies were rarely used, as described earlier.

Discussion

While a number of advanced prehospital emergency medical services systems rely partly or wholly on the use of preprinted protocols by field paramedics, many systems insist that the care of individual patients be directed by physicians or specially trained nurses who communicate with field personnel through sophisticated equipment.[1,2] This allows direct control in each instance to be maintained by highly trained personnel; theoretically, such physicians and mobile intensive care nurses could tailor interventions to the specific needs of individual patients. On the other hand, there are a number of important potential disadvantages to this on-line approach: decisions made by individual practitioners with more or less experience in prehospital medicine may be less optimal than those established generically by experts in this field[5,6]; radio contact takes time,[7] as does the decision-making process on the part of hospital personnel (although frequently this merely involves a mobile intensive care nurse reading from the same type of algorithm that could be supplied directly to field paramedics); errors of omission and even of commission on the part of paramedics are difficult to identify, requiring a laborious review of individual cases, which often cannot distinguish what was done because of base-hospital idiosyncrasy from what paramedics may have elected to do on their own. Finally, there is a tremendous financial cost attributable to both the development and maintenance of an on-line communication system and the training and maintenance of a large number of designated personnel involved in local supervision and quality assurance review of paramedics.[3]

Paramedics using standing orders predefined by medical experts in the area of prehospital care could proceed directly to providing care for patients with given presentations, without having to first take the time to establish radio contact with a base hospital.[1] This has been shown to significantly diminish time at the scene of medical emergency.[7] Standing orders could ostensibly be based on the most informed opinion of the most knowledgeable physicians.[5] A failure of paramedics to follow protocols precisely could be easily tracked by computer programs designed to correlate the recommended approach for any given patient complaint and care actually provided.[8-10] For these reasons off-line medical control for patient care rendered by the system as a whole would be improved, rather than lessened, by removing most decisions from local individual providers. Cost savings, as will be discussed, would be dramatic.

In any case, even possible benefits of universal on-line control are meaningless if patient care actually provided virtually never varies from standard protocols in any important way. Our data show that in most patients with the four common and representative chief complaints we reviewed—which make up a substantial portion of our nontraumatic call load—important base-hospital input is rarely needed. Deviations from standard protocols were infrequent and usually based on easily identifiable criteria, such as notably abnormal vital signs, profuse diaphoresis, or pulmonary rales. Other extremely unusual cases of protocol deviation, such as the use of a hypertonic glucose solution in patients with a normal mental state or lidocaine in patients without any apparent indication, did not seem to contribute in any way to patient care and suggest a diminution in the level of care provided, rather than a special benefit accorded patients by the availability of on-line medical control.

A prehospital emergency medical services system designed to allow for selective base-station contact as determined by protocol, involving both predefined criteria (such as abnormal vital signs or the presence of profuse diaphoresis) and paramedic judgment (paramedics should be free to obtain help when concerned about an individual patient) would be far better and more efficient than our current model. As many as 90% of current base-station contacts would be avoided, allowing for substantial decreases in the number of facilities required to maintain expensive base-hospital facilities, while the remaining units would still be required to deal with only a similar manageable number of calls. As a separate benefit, paramedic field times would undoubtedly decrease, without affecting decision making for the vast majority of patients, while physician input would remain available for those few patients for whom it might be beneficial.

The cost savings involved would be striking because current expenditures required to maintain a paramedic base station in Los Angeles are estimated to exceed $210,000 each year.[3] The lion's share of these costs are related to personnel, and a number of the positions involved, such as paramedic liaison nurse, and activities, such as data collection, continuing education, and quality assurance, are mandated by the Los Angeles County Department of Health Services. Mobile intensive care nurses must also be trained to handle the radio, given time to answer calls and enter data into the countywide data collection system, paid a salary differential for their expertise, and sponsored—with both time and money—for continuing education necessary to maintain that status. The average time spent by these nurses in our department on each paramedic run is more than 20 minutes (E. Igarashi, RN, MICN, unpublished data, October 1987), which translates into more than 700 hours (equivalent to 6 full-time staff) each month; this does not include time spent on other required activities described earlier. A full-time paramedic liaison nurse who is highly trained and appropriately compensated is mandated for each base hospital by the Los Angeles County Department

of Health Services to supervise base-station activities, quality assurance, and education. Every base hospital must also retain a physician director whose important responsibilities in this regard may not be directly compensated but do require substantial time input. Secretarial support is also required for the mandated data collection activities. Total personnel expenditures are thus estimated to exceed $150,000 each year.

Other costs include the maintenance of telecommunication hardware (estimated to cost $16,400 annually per base station), the training of base-station physicians (not included in cost estimates), and the resupply of paramedic units ($11,000 annually, but not likely to change regardless of the number of base hospitals or frequency of radio use). The cost initially to install the necessary radio equipment is about $62,000; this cost is not even included in the more than $200,000 calculated annual outlay.

While we have evaluated only four of the more common chief complaints, there is evidence to support similar reasoning for other categories of prehospital patients. Given the limited value of any intervention other than early defibrillation for the treatment of cardiac arrest,[11-16] it is not surprising that an adherence to protocols appears to be at least as efficacious as a selected deviation from such protocols in the prehospital management of this problem.[1,17] With regard to the prehospital management of trauma, there is controversy as to whether advanced life support is even preferable to "scoop and run"[18]; even advocates of prehospital advanced trauma life support often dismiss the need for on-line communication with hospital personnel.[19,20] Even with presentations where differentiating the diagnosis is notoriously difficult, such as shortness of breath, hospital personnel depend on paramedic assessment to determine treatment, and this assessment is often ultimately found to be incorrect.[21] Protocol treatments can take this into account by mandating therapy least likely to be harmful in the case of other causes of the symptom involved.[21]

While we have no reason to think that the same observations would not apply to many other cases, we acknowledge that it is premature (if not impossible) to attempt to generalize our findings to all prehospital chief complaints. Nevertheless, even if only 75% of chief symptoms are amenable to a system employing a selective use of prepublished protocols, and if for these symptoms paramedics ended up making such contact 25% of the time, the total communications load could be reduced by more than 50%; this could result in annual savings on the order of $3 million in Los Angeles alone. All this could be accomplished without any apparent decrement in the care provided to patients, with a likely decrease in time spent in the prehospital environment, and with a likely increase in the closeness of medical control provided for the system as a whole. Current emergency medical services systems such as those in place in Los Angeles and most of California deserve being reevaluated along these lines.

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Conferences and Reviews

Therapeutic Cardiac Catheterization in Children

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Presented in part as Grand Rounds at the Children's Hospital of San Diego, October 9, 1987, and at the UCSD Medical Center, April 4, 1988.

Cardiac catheterization, once the mainstay of diagnosis in children with congenital heart disease, has become a therapeutic modality for many conditions. Balloon dilatation can now open stenotic valves and vessels, coils and umbrellas can now close unwanted communications, and emboli can be withdrawn without surgical intervention.

(Waldman JD, Swensson RE: Therapeutic cardiac catheterization in children. West J Med 1990 Sep; 153:288-295)

From the introduction of a catheter into the human vascular system in 1929[1] through the work of Andre Cournand (for which he was awarded the Nobel prize in 1956) to the present, cardiac catheterization has been used as a diagnostic tool. In the late 1960s, pediatric cardiologist William Rashkind, MD, first used catheterization as a therapeutic modality,[2] and recent advances have expanded the use of this technique. In this report, we summarize the current status of therapeutic cardiac catheterization in children, with specific reference to the experience at the San Diego Regional Pediatric Cardiac Program (Table 1).

Creating an Atrial Septal Defect

Initially done to create a low-pressure site for intercirculatory mixing in patients with transposition of the great arteries, balloon atrial septostomy is now also used when there is stenosis or atresia of an atrioventricular valve in order to decompress the obstructed side of the heart. The technique described by Rashkind and Miller in 1968 has been only minimally changed over the years,[3] but modern ultrasound technology can noninvasively assess the location and size of the tear in the septum primum[4] as well as quantify the interatrial flow.

From 1978 to 1989, balloon atrial septostomy has been carried out in 147 neonates and infants. Most (84%) had transposition of the great arteries. In four the procedure was unsuccessful: three had a hypoplastic left-heart syndrome and the left atrium was too small to accept an inflated balloon, and one newborn with transposition of the great arteries and bilateral left-sided atrial appendages died of a tear in the base of the anomalously originating right atrial appendage. Two patients had complete heart block resulting from the procedure. Excellent palliation was achieved in 96%, and this high success rate can be related partly to the use of large volumes (average, 4 ml) in the balloon and partly to the performance of the procedure by experienced attending physicians.

A newer technique for creating an atrial septal defect was developed by Park and colleagues in 1978.[5] By using an extendable and retractable blade at the catheter tip, the atrial septum is incised rather than torn. This procedure is useful in those with a thick atrial wall, especially older children. After a blade septotomy, a balloon septostomy technique is used to enlarge the defect. We have used this combination approach in six patients: four with pulmonary atresia and an intact ventricular septum and two with transposition of the great arteries. No problems were encountered, and each child received adequate palliation.

Closing an Atrial Septal Defect

Just as in some patients an interatrial communication is needed, in others—that is, patients with naturally occurring defects in the atrial septum—the communication may be closed nonoperatively. This has been tried using various devices,[6,7] the most recent being a biconvex ("double clamshell") apparatus that shows promise in initial trials. Results must be judged, however, in comparison to a surgical procedure that has essentially no morbidity or mortality. Transcatheter closure of atrial septal defects remains at present an experimental procedure with which we have had no experience.

Balloon Dilatation

The technique for balloon dilatation is similar in most lesions, the major difference being the calculation of the appropriate (safe but effective) balloon size. After baseline hemodynamic studies and angiography, an end-hole-tipped catheter is manipulated across the obstruction and a long (exchange) wire is fed through the catheter into the distal vessel or chamber. The catheter is then removed, leaving the wire in place, and the balloon dilatation catheter is advanced over the wire until the balloon is centered over the stenosis. The balloon is then inflated rapidly several times to a very high pressure in the hope of tearing the obstruction (valve or vessel) without causing rupture. Hemodynamic studies and angiography are repeated, with the contrast dye being injected well away from the dilated (and therefore weakened) area.

Native Pulmonary Valve Stenosis

Balloon dilatation is now recognized as the procedure of choice in correcting stenosis of a native (as opposed to a prosthetic) pulmonary valve.[8] The technique and results have been well described.[9,10] Using balloons 40% to 50% larger than the pulmonary anulus,[11] it is possible to nearly obliterate the gradient (Figure 1) by tearing the fused valve tissue along the incomplete raphe.[12]

In our program, 51 children have had balloon dilatation

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of native pulmonary valve stenosis. No problems were encountered with any procedure. Each had a systemic or suprasystemic pressure in the right ventricle with gradients of 40 to 105 mm of mercury. Echocardiography interfaced with Doppler flow analysis proved extremely accurate in identifying the need for balloon dilatation and in measuring the anulus for the choice of balloon size. A reduction in both the gradient (Figure 2) and the right-left ventricular pressure ratio was noted in all cases; 31 (61%) had gradients after dilatation of less than 20 mm of mercury, and 11 of the 51 (22%) had gradients of less than 10 mm of mercury after the "pulmonary valvotomy without thoracotomy." Some patients were seen to have muscular subpulmonary narrowing on the echocardiogram taken immediately after the procedure; this dynamic obstruction generally resolved with time and may account for the transient residual gradients.

Reported short-term follow-up indicates that the low gradient after balloon dilatation either persists or can even regress further spontaneously[13]; our experience supports this observation. Long-term follow-up—over decades—is unavailable, but it seems likely that balloon dilatation will remain the procedure of choice for correcting stenosis of the pulmonary valve.

TABLE 1.—*Experience With Therapeutic Cardiac Catheterization (TCC) at the San Diego Regional Pediatric Cardiac Program, 1978-1989*

Types of TCC	*Procedures, No.*
Creation of atrial septal defect	
Balloon septostomy	147
Blade septotomy	6
Balloon dilatation of	
Native pulmonary valve	51
Native aortic valve	22
Recoarctation of the aorta	24
Porcine "pulmonary" valve	10
Branch pulmonary arteries	13
Mitral valve, rheumatic	2
Obstruction to superior vena cava	1
Discrete subaortic stenosis	2
Pulmonary vein stenosis	0
Closure therapy	
Atrial septal defect	0
Patent ductus arteriosus	6
Arteriovenous malformations, collaterals	6
Retrieval of intravascular embolus	5

Coarctation of the Aorta

After initial successes with balloon dilatation in unoperated children with coarctation,[14-17] concern was raised about the incidence of aortic aneurysms at the site of balloon dilatation.[18-21] At this time, the controversy is still unresolved as to the appropriateness of the procedure in these children, especially as the risk of balloon dilatation may be higher than of an operation. By contrast, there is general unanimity that balloon dilatation is the preferred approach to residual or recurrent coarctation for two reasons[22,23]: scarification in the operative area makes disruption or aneurysm of the aorta unlikely, and reoperation on the same site carries a higher risk of morbidity and a lesser chance of success.

Balloon dilatation of recurrent coarctation has been done in 24 patients in our program. Of these, 23 were successful (Figure 3). The single failure occurred in a 28-year-old man, 24 years after surgical repair. Despite the use of two large balloons, the lateral pressure delivered may have been inadequate to achieve a therapeutic tear in the stenotic vessel wall.

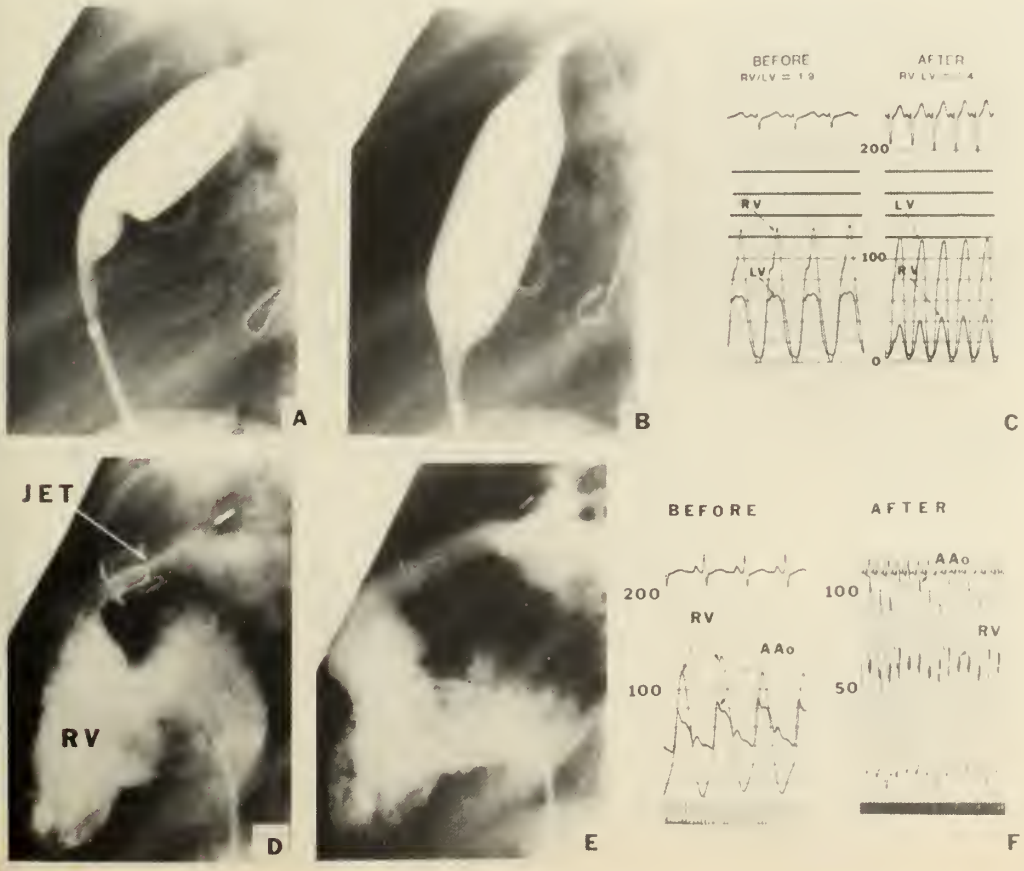

Figure 1.—Balloon dilatation (BD) is used to correct pulmonary valve stenosis, native or artificial. In a patient having BD of stenosis of a native pulmonary valve, **A,** the balloon, indented by the stenotic native pulmonary valve, is not in the proper position for BD as the midpoint of the balloon should be at the location of maximum obstruction. **B,** Having been pulled to a more proximal position, the balloon is inflated under high pressure, obliterating the "waist" or narrowing caused by the stenotic valve. **C,** The pressure change effected by BD converts the right ventricular (RV)-left ventricular (LV) pressure ratio from 1.9 to 0.4, decreasing the RV systolic pressure from 130 to 45 mm of mercury. In a patient with a stenotic RV-pulmonary artery porcine-valve conduit, RV angiogram **D** shows a "jet" through a stenotic porcine valve in the pulmonary position. **E,** After BD of the porcine valve, a large bolus passes through the valve. The conduit shows no evidence of pseudointimal proliferation. **F,** Before BD, the RV pressure is 120 with an ascending aortic (AAo) pressure of 85 to 90 mm of mercury. After BD, with the scale changed to 0 to 100, the RV-AAo pressure ratio is 0.6 with a systolic RV pressure of 65 mm of mercury, essentially half the pre-BD value. The angiograms **(A, B, D, E)** are all lateral views.

Native Aortic Valve Stenosis

In theory, balloon dilatation to correct aortic valve stenosis is an excellent alternative to surgical aortic valvotomy because it is precise and avoids the use of a median sternotomy.[24-26] But it is often done on the sickest infants, is technically demanding, is traumatic on the femoral vessel(s), may result in considerable blood loss, and carries a reported complication rate of 40%,[27] the highest of all balloon dilatation procedures. Thus, while balloon dilatation may be considered a reasonable alternative to surgical intervention in isolated cases of valvar aortic stenosis, it should be approached with considerable caution, and the parents must be well informed of all the risks involved.

In our center 22 children have had balloon dilatation for aortic stenosis, including a 2.5-kg neonate with severe low cardiac output and two infants aged 3 and 4 months (Figure 4). The average gradient was reduced from 64 to 30 mm of mercury. One child died of a probable ventricular dysrhythmia six hours after a balloon dilatation that was confirmed to be anatomically successful at autopsy. No child had significant aortic regurgitation (Figure 5) after balloon dilatation, but 5 of 21 (24%) survivors had complications—cardiac arrest, blood loss requiring transfusion, permanent loss of femoral pulse—supporting the contention by Fellows and colleagues that balloon dilatation for aortic stenosis has the highest morbidity rate of all such procedures.[27] It is too early to assess the moderate-term effect in these children, but 17 of the 21 survivors have not required an operation during a follow-up of as long as 28 months.

Stenosis of a Bioprosthetic 'Pulmonary' Valve

We have used balloon dilatation for stenotic porcine valves[28] within right ventricle-pulmonary artery conduits in ten children. Although a substantial reduction in the right ventricular pressure was usually achieved, angiography after balloon dilatation of the valve often showed additional obstruction at a conduit-branch pulmonary artery anastomosis; this was also dilated. In eight of ten patients, the conduit replacement could be deferred. It is important to seek out distal stenoses that may not be apparent until after the valve has undergone balloon dilatation. In one child, a circumferential tear occurred in the balloon, necessitating a femoral cutdown to remove the catheter; no problems were encountered in the other nine children. Calcified conduit valves may predispose to circumferential balloon tears or an embolus of a balloon fragment.[29]

Branch Pulmonary Artery Stenosis or Hypoplasia

Balloon dilatation of stenotic or hypoplastic pulmonary arteries[30,31] was done 13 times in nine patients. Eight children had postoperative obstruction following the correction of cyanotic congenital heart disease; adequate relief was accomplished in five.

One child with congenital hypoplasia of the pulmonary arteries had two successful balloon dilatations (Figure 6) but sustained a rupture of the left pulmonary artery at the third one; he required emergency surgical repair from which he recovered well. Congenital pulmonary artery hypoplasia is fundamentally different from postoperative obstruction. The therapeutic effect of balloon dilatation is accomplished by creating a transmural arterial tear through the intima and into the media (see Figure 6-C)[32]; vascular integrity is preserved by the adventitia. When a patient has had an operation, the area surrounding the obstruction has been dissected and manipulated, with resulting scar tissue. In contrast, a congenitally hypoplastic artery has no surrounding scarification and the walls may be thin between the bands of obstruction. Thus, balloon dilatation of postoperative branch pulmonary artery stenosis appears to have a relatively low risk, but the same procedure of congenitally hypoplastic pulmonary arteries may pose a higher risk.

A recent preliminary report provides some encouragement for patients with congenital peripheral pulmonary artery stenosis because of the successful insertion of internal stents to maintain the expanded internal dimension and avoid restenosis.[33] It is hoped that this technique will soon be available for expanded clinical trials.

Rheumatic Mitral Valve Stenosis

While successful balloon dilatation of congenital mitral valve obstruction has not been reported, good results have been obtained in patients with rheumatic mitral valve stenosis.[34-36] Technically, this requires inserting a long sheath across the atrial septum for placing the balloon dilatation system and often the use of two balloons simultaneously. Because rheumatic carditis is rare in southern California, we have seen only two children who were candidates for balloon dilatation of a stenotic mitral valve. Each child required two 20-mm balloons. Gradients of 19 and 21 mm of mercury were reduced to 5 and 7 mm of mercury, respectively. Each had a tiny residual atrial septal defect from the transseptal procedure, but the volume of left-to-right shunting was detectable only by color Doppler technology.

Obstruction to Systemic Venous Return

Occasionally after a venous switch operation for transposition of the great arteries, there is obstruction at the junction of the superior vena cava and right pulmonary artery or in the midportion of the new "right atrium." While success has been reported with balloon dilatation,[37,38] our

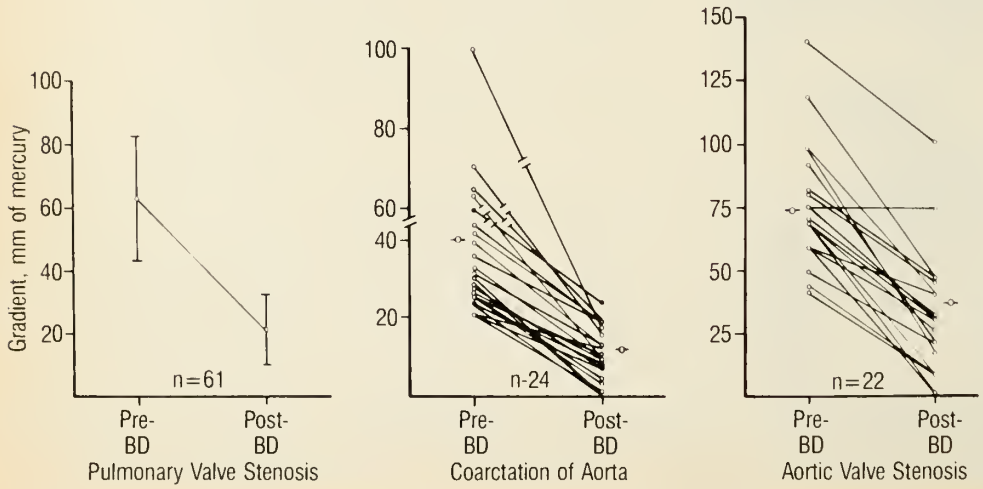

Figure 2.—Acute pressure changes are caused by balloon dilatation (BD). **Left,** In 61 patients (51 with BD of a native pulmonary valve and 10 with stenosis of a bioprosthetic valve), the average gradient was 64 mm of mercury before BD and 22 mm of mercury after BD. **Middle,** In 23 of 24 patients, the gradient across a recurrent aortic coarctation was reduced. Gradient reduction was more dramatic in those with greater pressure differences pre-BD. **Right,** In those with aortic valve stenosis, variable degrees of gradient reduction are noted. Several with minimal response to BD had more than 1 level of left ventricular outlet obstruction. -o- = mean values

experience showed that an initial good result may not persist over time.[39] Long-term follow-up is needed to determine whether this mode of treatment is truly useful.

Discrete Subaortic Stenosis

Reports from Spain and Columbia, Missouri, describe the successful use of the balloon dilatation technique for discrete subaortic stenosis in 17 children.[40,41] In our program, two patients have had balloon dilatation for subaortic stenosis, each for esoteric reasons: one was an illegal alien for whom funding was unavailable and the second had propionic acidemia, a metabolic disorder wherein the risk of an operation was considered prohibitively high. In both patients, echocardiography showed a substantial reduction in the anatomic obstruction; in the first child, other levels of left ventricular outlet obstruction made the gradient reduction small, and in the second child, the gradient was reduced by balloon dilatation to zero from 60 mm of mercury. Surgical repair continues to be the preferred option for subaortic stenosis but, in rare instances, balloon dilatation may be an acceptable alternative.

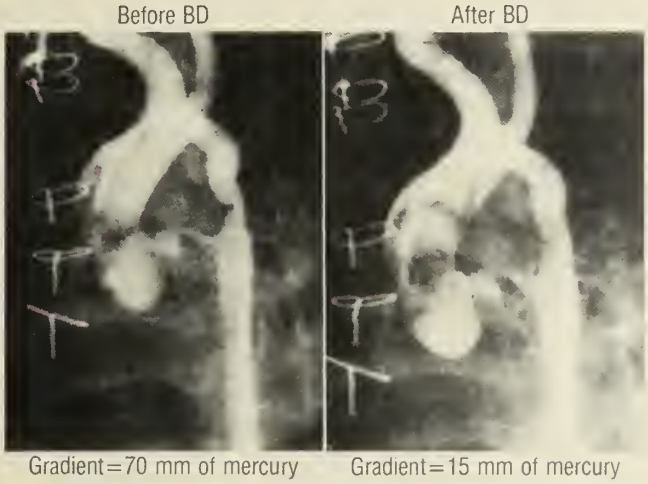

Figure 3.—Lateral angiograms taken of a patient having balloon dilatation (BD) for recurrent coarctation of the aorta show, **Left,** before the procedure, both discrete and long segment narrowing with a gradient of 70 mm of mercury from the right arm to legs. This patient had had a subclavian flap aortoplasty repair of coarctation at another center. Note the absence of the subclavian artery. **Right,** After BD, the aortic constriction is abolished and the gradient was reduced to 15 mm of mercury. (A dramatic clinical improvement occurred.)

Pulmonary Vein Stenosis

Pulmonary vein stenosis is a condition not surgically correctable, and, therefore, it was with considerable hope that balloon dilatation was applied to five children in Texas and six in Boston with this uniformly fatal lesion.[42,43] Although the results were initially successful, stenosis recurred in each case. Thus, no lasting benefit was provided by currently available balloon dilatation techniques. We have not attempted the procedure in any patient with pulmonary vein stenosis. As with pulmonary artery hypoplasia, internal stents may be useful in this condition.

Closure of Patent Ductus Arteriosus

Per catheter closure of persistent patent ductus arteriosus has been performed with various devices, including double balloons,[44] preformed plugs,[45] a plug plus an umbrella,[6] and a double-umbrella device—the Rashkind occluder[46]—that has recently been approved for clinical use by the US Food and Drug Administration. A combined report from Philadelphia, Pennsylvania, Houston, Texas, and New Haven, Connecticut, showed a success rate (complete closure) of 78% with an embolization incidence of 10%.[47] Even more recent data indicate a success rate in the 90% range with further modifications in technique (J. E. Lock, MD, oral communication, November 1989). Our experience in San Diego is limited. We have used the Rashkind occluder six times with good results (Figure 7) in four patients and embolization in two (one anticipated because of pulmonary vascular obstructive disease).

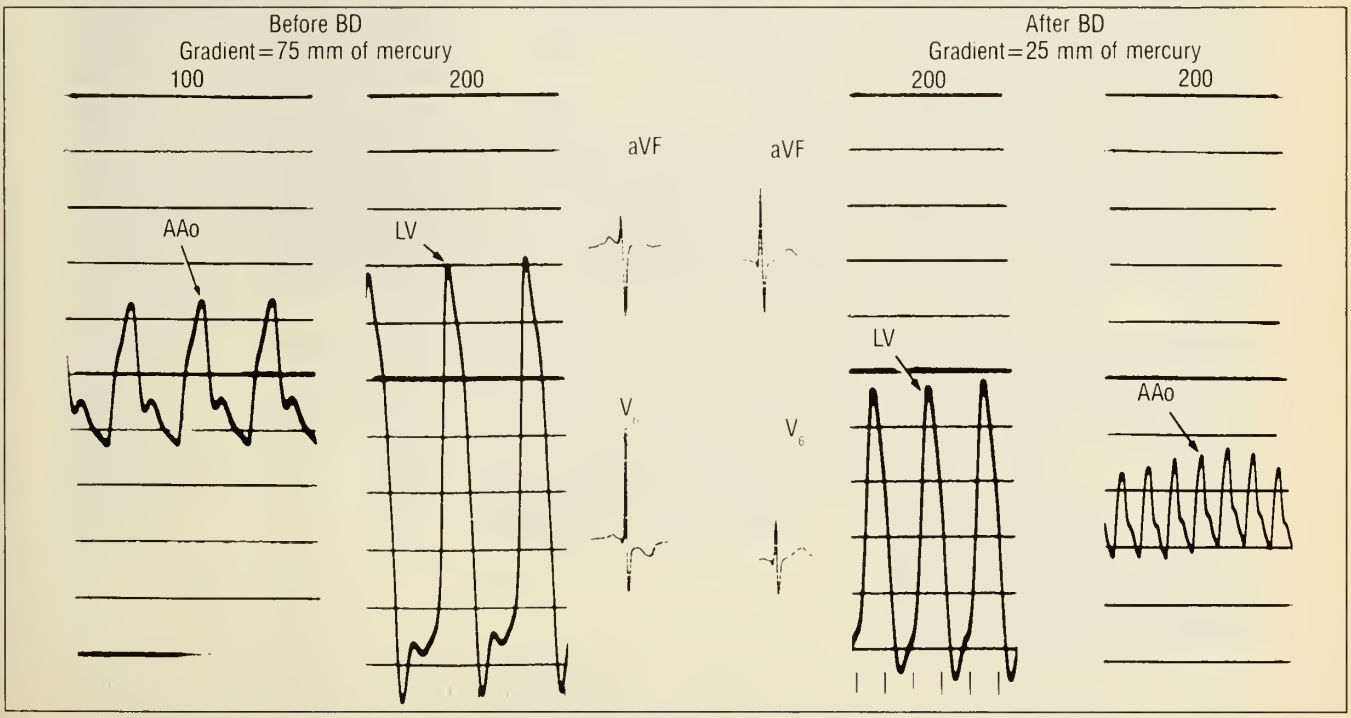

Figure 4.—A 3-month-old infant had balloon dilatation (BD) for aortic stenosis. **Left,** Before the procedure, the ascending aortic (AAo) pressure is 65 mm of mercury, and left ventricular (LV) pressure is 140 mm of mercury. There are inverted T waves in electrocardiographic leads aVF and V_6. **Right,** After BD, T waves are normal, and the LV-AAo gradient is 25 mm of mercury.

Embolus—Insertion or Removal

The insertion of various devices by catheter is a well-established technique in cancer therapy and for obliterating arteriovenous malformations.[48] It is now being used to close a patent ductus arteriosus or atrial septal defect as well as unwanted (residual) postoperative intercirculatory communications.[49] We have used coils to occlude hepatic hemangiomas, pulmonary arteriovenous malformations and aorta-to-pulmonary artery collateral vessels (Figure 7) in six patients with success in each.

Occasionally pieces of intravascular catheters are unintentionally severed, resulting in an embolus of the catheter tip. The retrieval of such foreign body emboli has long been known in adults[50] but is only rarely needed in children. On five occasions, a retrieval of catheter-tip emboli was attempted. In one neonate, the tip of an umbilical venous

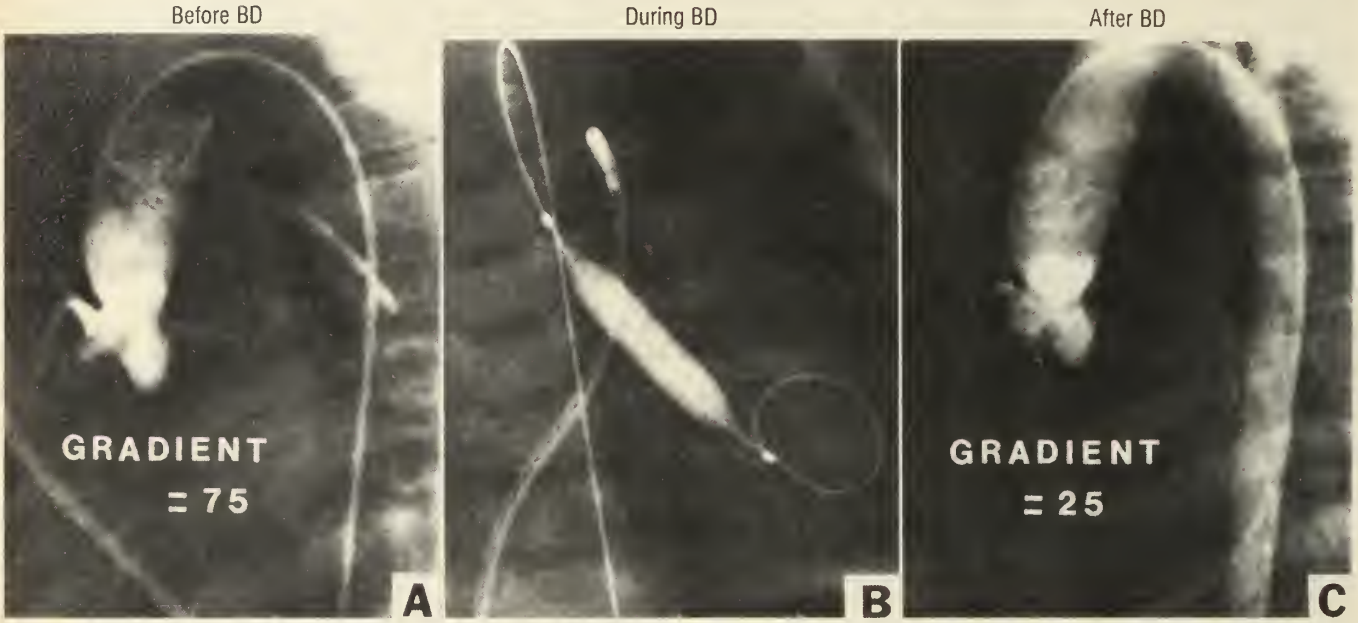

Figure 5.—Aortic valve competence is assessed in a 3-month-old infant having balloon dilatation (BD) for aortic stenosis. **A,** Lateral ascending aortogram shows an eccentric opening and no regurgitation. The gradient is 75 mm of mercury. **B,** A frontal view of the inflated 6-mm balloon shows obliteration of the waist. The loop of extra guide wire in the left ventricle provides an anchor for the BD catheter. **C,** After BD, with the gradient reduced to 25 mm of mercury, supravalvar narrowing is again apparent. The aortic valve continues to be competent.

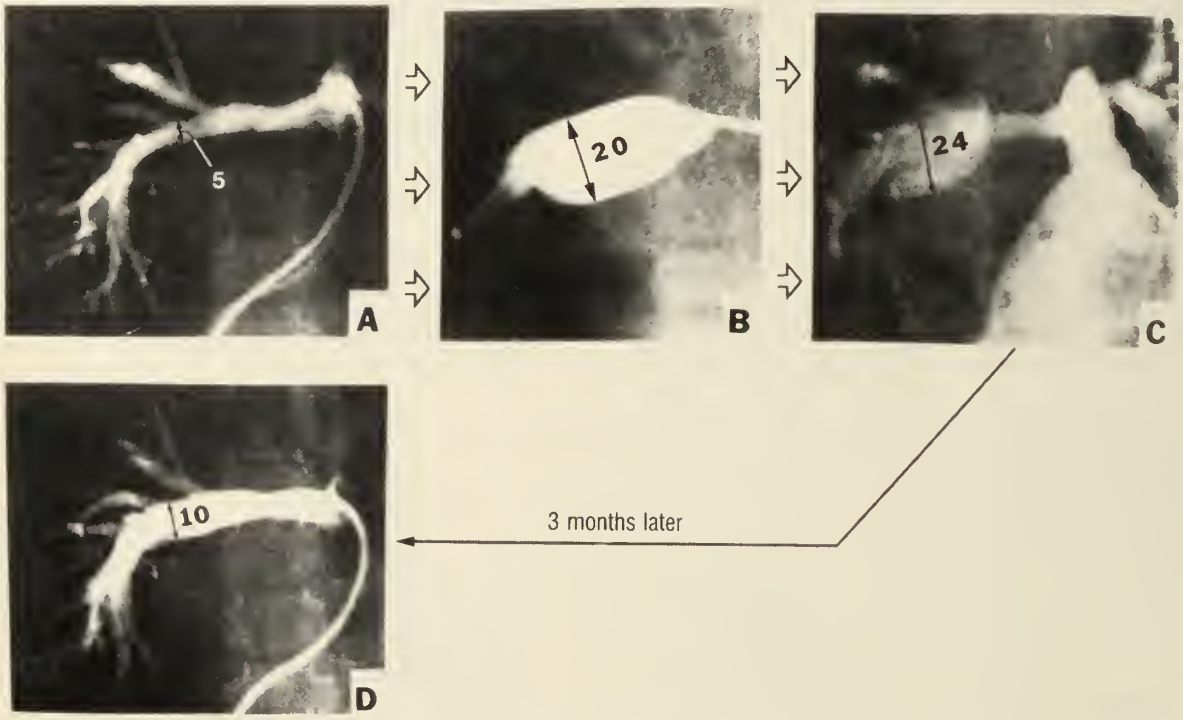

Figure 6.—Balloon dilatation (BD) was done in a 2½-year-old child with congenital peripheral pulmonary artery stenosis. **A,** The distal right lower pulmonary artery measures 5 mm in transverse diameter. **B,** After several BDs with balloons of increasing size, a balloon is used that is 4 times the size of the narrow segment. **C,** There is an "aneurysm" of the distal right pulmonary artery that measures 24 mm. The angiogram is performed in the right ventricle, with the contrast dye injected well away from the area that has been dilated. **D,** 3 months after BD, the right pulmonary artery measures 10 mm—twice the pre-BD size.

catheter had embolized into the liver and could not be retrieved because the umbilical vein was closed. In four other children with noncardiac disorders such as leukemia or hydrocephalus, a surgical procedure would have engendered considerable risk. A basket snare (Figure 8) or biopsy forceps was successfully used to remove an embolus from the pulmonary artery (three patients) and the right atrium (one child).

Therapeutic Cardiac Catheterization

There are several areas where therapeutic cardiac catheterization (TCC) will have considerable effects, such as in medical case planning, the bureaucratic and legislative arena, and in financial matters.

Medical Effects

With the addition of TCC to the armamentarium, planning for some congenital heart lesions has changed. In coarctation of the aorta, most recurrent or residual obstructions can be balloon dilated; therefore, tube graft-type repairs are now avoided. In tetralogy of Fallot, it is now of less concern to leave some residual branch pulmonary artery stenosis. In children with repaired truncus arteriosus in whom stenosis of the valve or distal anastomoses develop, balloon dilatation allows a deferral of conduit changes. Critical semilunar valve stenosis has become a "medical" rather than a surgical emergency.

Until TCC, congenital peripheral pulmonary artery stenosis was a lesion not amenable to therapy. The obstruction usually extends too distal in the lung for surgical repair. With the use of balloon dilatation, internal stents, or both, distal stenoses may be treated by catheter insertion, and residual proximal obstruction may be treated surgically.

Bureaucratic and Legislative Effects

The use of therapeutic cardiac catheterization requires consideration by state regulatory agencies. Without approval of, for instance, California Children's Services in California, third-party payers will not reimburse for the service, precluding the use of the less expensive TCC approach in favor of the more traditional but costlier surgical alternative. As for surgical treatment or cardiac catheterization, standards for training need to be developed. Therapeutic cardiac catheterization is not a procedure that can be read about in a paper and then performed safely. Furthermore, an ongoing monitoring process is necessary to assure quality.

At present, numeric guidelines for diagnostic cardiac catheterizations and for surgical procedures are used to determine accreditation of licensed cardiac centers. The use of TCC will increase the number of catheterizations and decrease the number of operations. Of 640 cardiac catheterizations done in 1987 and 1988, 113 (18%) were done primarily for therapeutic purposes; the number of

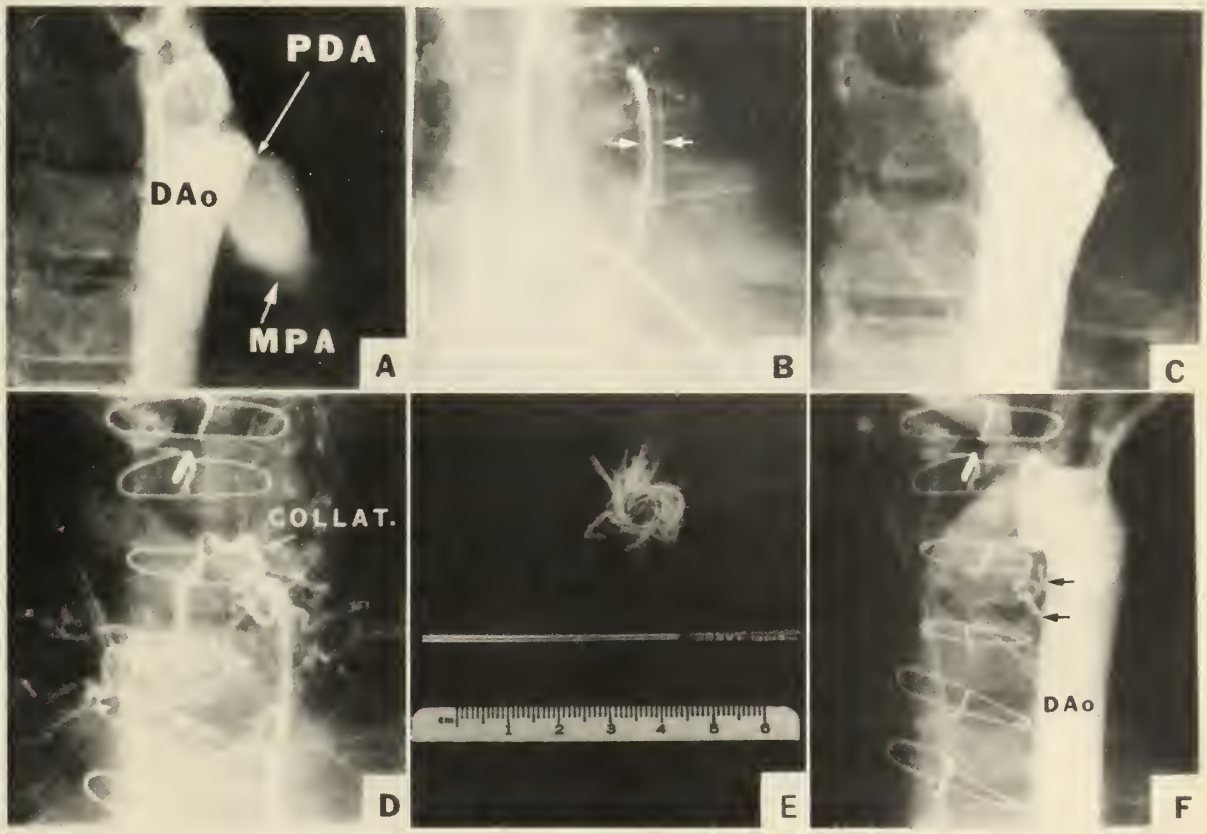

Figure 7.—"Embolotherapy" is used to close a patent ductus arteriosus (PDA) **(A, B,** and **C).** The aortograms in the top row of photos are frontal views. **A** and **C** (from the same patient), A 12-mm Rashkind occluder was inserted; this is almost invisible radiographically. A 17-mm device from a different patient is shown in **B. A,** Contrast dye injected in the descending aorta (DAo) shows the PDA filling the main pulmonary artery (MPA). **B,** The arrows indicate the large sheath used to guide the collapsed device into position. The device is seen with proximal and distal "legs" expanded, still attached to the delivery system. **C,** Following insertion of the Rashkind occluder, no contrast is seen to pass into the pulmonary artery from injection in the (aortic) ductal infundibulum. A patient with tricuspid atresia had embolotherapy after a Fontan procedure **(D, E,** and **F). D,** A subselective angiogram shows a collateral vessel (collat.) from the descending aorta to the right lung, which creates a left-to-right shunt. **E,** The device at the top of photo is used for embolization; the coil holds the thrombotic strands in place. The lower object is the metal tube used to keep the coil straight for inserting into the delivery catheter. **F,** A descending aortogram after therapeutic cardiac catheterization reveals 2 metallic coils **(black arrows)** placed per catheter that occlude the two right-sided collaterals, one of which was shown in **D.**

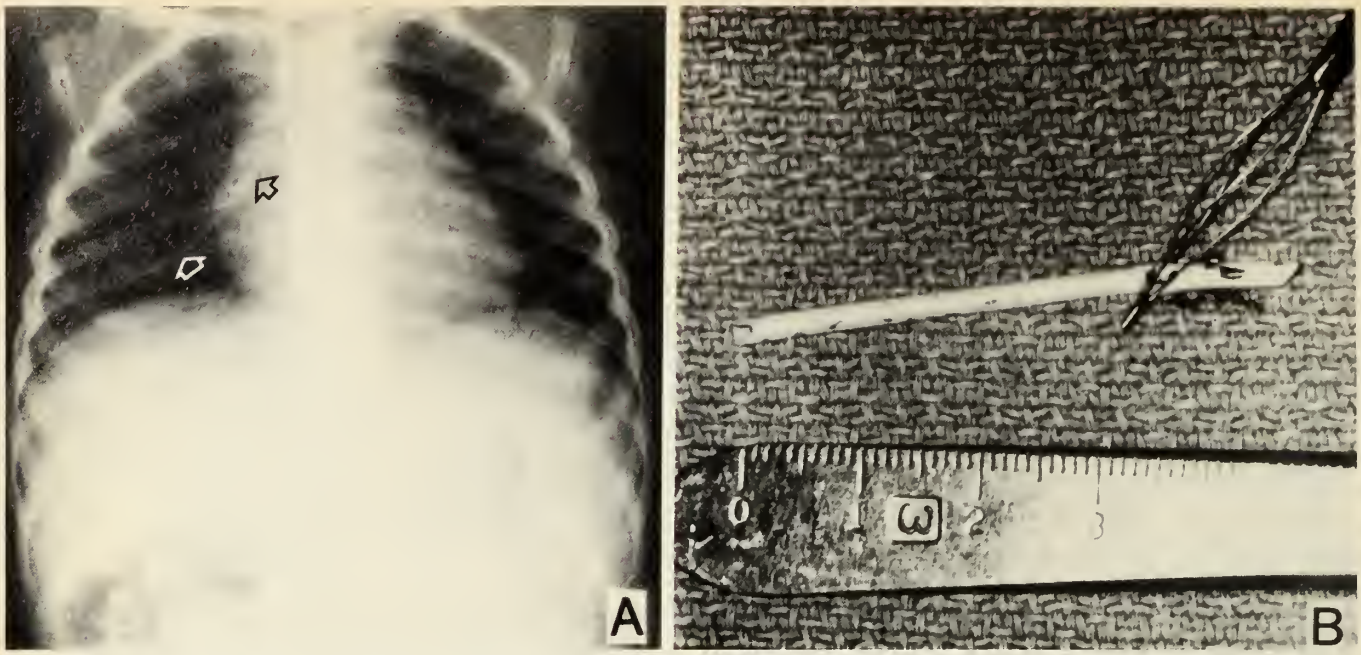

Figure 8.—The photos show catheter retrieval of a catheter-tip embolus. **A,** A segment of Broviac catheter is lodged in the right lower pulmonary artery **(arrows). B,** The Lehman catheter, basket snare, and retrieved catheter-tip embolus are seen.

catheterizations has therefore increased by that number, and the surgical volume has decreased by a corresponding number. These factors also require consideration by state advisory or regulatory agencies.

Fiscal Effects

Treating congenital heart disease is expensive. The surgical repair of "simple" problems such as patent ductus arteriosus can cost around $10,000. The surgical repair of critical semilunar valve stenosis, ventricular septal defect, or tetralogy of Fallot can cost well over $30,000. Balloon dilatation catheters are relatively expensive ($250 to $350 each), and some procedures require more than one. The charges for TCC are usually added to the charges for a diagnostic study, thus increasing the cost of the procedure itself. Although diagnostic catheterizations are routinely done at our center with same-day discharge,[s1] patients having TCC stay overnight for observation and postprocedure tests that include a complete blood count, a chest roentgenogram, and an echocardiogram or pulmonary perfusion scan (or both). Thus, a child with pulmonary stenosis who undergoes balloon dilatation spends 1½ days in hospital with an average hospital bill of $3,800 (Figure 9). A comparable patient who had an open-heart procedure for the surgical relief of pulmonary stenosis spent 7½ days in hospital with an average total hospital bill of more than $21,000. The disparity can be even more dramatic in critical neonatal semilunar valve stenosis. Each of our infants who had balloon dilatation of aortic stenosis went home within four days.

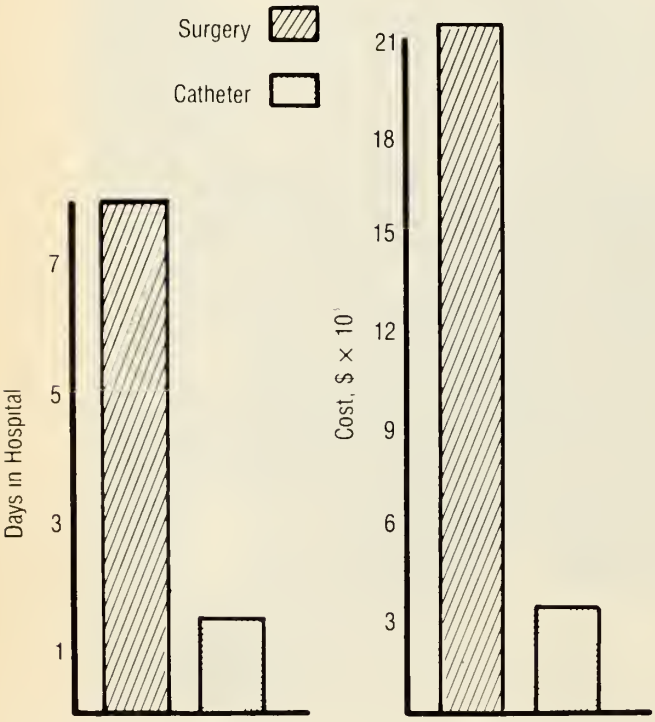

Figure 9.—Balloon dilatation (catheter therapy) is compared with surgical treatment of valvar pulmonary stenosis. In the left graph, the average hospital stay is 7½ days for the surgical relief of pulmonary stenosis; catheter therapy requires 1½ days in hospital. The right graph shows that the cost of an operation is $21,300 (average), compared with $3,800 for balloon dilatation.

Though the case incidence in which TCC will replace surgical treatment is relatively small (approximately 15%), the fiscal impact of TCC can be substantial. For an individual center, the fiscal effect of TCC can be calculated as follows: average number of operations per year × 0.15 × 0.2 equals the percentage decrease in cost of therapy for congenital heart disease. This translates into a large dollar savings for the state when multiplied by the number of centers doing TCC.

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Overview of Hemochromatosis

LLOYD H. SMITH, Jr, MD, *San Francisco*

Hemochromatosis is a unique genetic disorder, or possibly a group of disorders, whose phenotypic expression is that of continued excessive absorption of dietary iron.[1-4] As a result, the body's iron stores typically increase markedly (Figure 1). The clinical manifestations of the disease result from damage to those organ systems in which iron has been pathologically deposited, most commonly the liver (cirrhosis), pancreas (diabetes mellitus), anterior pituitary (gonadotropin deficiency), heart (cardiomyopathy), and joints (arthritis). Hemochromatosis is one of the most common genetic disorders of whites. The diagnosis is frequently missed, however, because the early clinical manifestations of hemochromatosis are often subtle and atypical. Furthermore, many patients, especially women, do not develop any disability despite being homozygous for this condition. An effective, simple treatment is available, that of iron removal by phlebotomy; it is therefore particularly important that physicians become much more knowledgeable about this common disease.

Historical Background

Hemochromatosis received its name from von Recklinghausen exactly 100 years ago.[5] As is so frequently true, however, earlier descriptions can be traced to others, such as Trousseau and Troisier. Sheldon first suggested that hemochromatosis was an inborn error of metabolism and elaborated upon this theme and the clinical and pathologic description of hemochromatosis in his monumental monograph in 1935.[6] Twenty years later Finch and Finch further clarified the definition of the disease and the usefulness of iron depletion therapy by phlebotomy.[7] Over the succeeding years many investigators have contributed to our understanding of normal iron metabolism and the abnormalities characteristic of iron storage disorders. The genetic transmission of hemochromatosis remained unclear, however, until the seminal discovery by Simon and his colleagues of the close linkage of the phenotypic expression of hemochromatosis with HLA-A.[8] This has allowed the definitive demonstration that hemochromatosis is transmitted as an autosomal recessive disease. The last decade has witnessed new insights into the prevalence of hemochromatosis and the intricacies of iron metabolism at both the cellular and molecular levels. The basic abnormality of hemochromatosis still awaits elucidation, however.

Key Questions

As an "inborn error of metabolism," to use Garrod's venerable term, or as an autosomal recessive genetic disease, as it is now known to be, hemochromatosis produces a characteristic metabolic derangement. Most metabolic diseases are diseases of "too much" or of "too little." Hemochromatosis, a disease of "too much," is thought to be simply an inappropriate avidity for the absorption of dietary iron with resulting tissue damage from its pathologic deposition. Despite the advances of recent years, however, a number of questions remain:

1. What is the gene product, encoded on chromosome 6, the absence or defective nature of which leads to excessive absorption of iron?
2. What is the normal function of this presumed protein in controlling iron absorption? For example, is it expressed and does it function in the intestinal mucosal cell? Or is it a signal protein (i.e., a hormone) that informs the mucosal cell about the body's need for iron (the level of body stores or the rate of erythropoiesis)?
3. Is the pathophysiologic abnormality solely in the absorptive mechanism for dietary iron or are there additional abnormalities elsewhere in the internal economy of iron metabolism?[9]
4. Why has this genetic disorder persisted at such a high prevalence in whites?
5. How does excessive iron injure cells and thereby lead to the manifestations of the disease?
6. How can the diagnosis best be made? Should we screen routinely for this relatively common disorder?
7. Why does hemochromatotic liver disease so frequently lead to hepatoma?

These are but some of the questions that remain despite the rapid advances of the past decade.

Normal Iron Metabolism

An understanding of the abnormal metabolism of iron that is the hallmark of hemochromatosis requires a brief description of its normal metabolism.

State of Iron in the Body (Figure 2, Table 1). The average adult has approximately 3 to 4 grams of body iron.[10] Of this approximately two thirds is functional, largely in the heme groups of hemoglobin and myoglobin but also in the cytochromes, peroxidases, catalase, and other enzymes. There is no evidence of abnormalities in the synthesis of these iron-containing constitutents in hemochromatosis except as a nonspecific secondary effect of tissue damage, such as in cirrhosis. Storage iron (~ 1.0 g) is predominantly found in two forms—in ferritin and in hemosiderin.

Ferritin is a large (480,000 dalton), complex protein consisting of 24 subunits that combine to produce a shell around a core that is specialized to receive and bind iron as ferric hydroxyphosphate.[1] As many as 4,500 atoms of iron can be stored within a single ferritin molecule, to be released as needed for functional purposes. In fact, a number of ferritins exist in different organs, consisting of different mixes of H and L subunits, but no clearcut functional differ-

(Smith LH Jr: Overview of hemochromatosis. West J Med 1990 Sep; 153:296-308)

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This work has been previously published as an update to the CECIL TEXTBOOK OF MEDICINE, WB Saunders, Philadelphia, and sponsored by Key Pharmaceuticals, makers of NORMODYNE (labetalol HCl) tablets.

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Journal of the Arizona Medical Association

ARIZONA MEDICINE

September 1990, Vol. XLVII, No. 9

Marshall B. Block, M.D.

Who's Going to Look Out For Me?

During what I thought was going to be a routine phone call from my parents, I was informed that my mother was going to have cataract surgery. Two days before the procedure was to be done, I received a frantic phone call in the middle of the night from my father who said, "I was asleep and I had this dream that someone was holding down my arms while someone was breaking into our apartment. I tried to wake up but couldn't, and I felt this pressure on both of my arms. I thought I was paralyzed! The pain in my arms is still there--do you think it's my heart?" I then tried to reassure my father that all he had was a "bad dream" and that his arm pain probably didn't represent heart disease. However, I was concerned about the content of the dream and told him that mother was going to be fine and nothing was going to happen to her during her planned surgery. His response, as usual, floored me. He said, "Your mother! Who's going to take care of me if something happens to her? Your sister is in New York and you are in Arizona and I'm going to be here all alone!" Thankfully, my mother is a strong woman and has a positive attitude and ignores much of my father's fears. Happily, she sailed through the operation and their interdependence continues, to the relief of my sister and I. Nevertheless, the episode brings out an underlying selfish concern we all should be developing in this period of uncertainty as modern medicine evolves.

For practical discussion, one can divide the current physician pool within the United States into several age groups. Those age 60 and older really have no major concern as practitioners, for most of the changes which are, and will take place within the next five to ten years in medicine, will not materially affect them. Most will either retire or, if necessary, close their fee-for-service practice and enter into some sort of contractual arrangement with a major health care provider until their retirement occurs. The largest group of physicians are those between the ages of 40 and 60. These physicians face the most stress as our health care system evolves. Many of these physicians have been in fee-for-service medicine for at least ten and most fifteen to twenty years. They have a significant emotional and intellectual investment in our current health care system and are the ones who are probably most recalcitrant to the current changing environment. They are the ones who will be most affected by an inevitable declining income and self worth as controls, both financially and professionally, are set into place at multiple levels. Those physicians between ages 30 and 40 are probably just entering practice or have been in practice a short period of time. They have grown up within the hurricane of medicine and have no fixed ideas or preconceived notions which will impede their adaptation to the uncertainties of the future. Those currently in training will, likewise, not have a difficult time as they mature and enter the provider network.

Thus, we must direct some attention within our profession to the stresses and strains that will be placed upon those physicians in the mid-point of their careers. Their responsibilities outside of medicine are at their maximum as well. Most are married, most have families, and most are involved in outside activities. The financial strain of teenagers and college-aged students increases dramatically during this phase of life. Maintaining a constant life style becomes increasingly difficult under the current changing system with fixed costs remaining constant or increasing at or above inflation rates. Coupling this with diminishing "patient psychic rewards" as the health care system moves from "free choice" to "book choice" and increasing fears of financial disaster if a mistake is made, due to our current tort system, produces an undercurrent within each of these physicians. This can and does affect their emotional stability and health. Just when one appears to be reaching the zenith of professional growth, financial security, emotional maturity and familial responsibility, everything can come "tumbling down."

Continued on page 10

Journal of the Arizona Medical Association

ARIZONA MEDICINE

September 1990, Vol. XLVII, No.9

Arizona Medicine is a socioeconomic and scientific journal published monthly by the Arizona Medical Association, Inc., 810 West Bethany Home Road, Phoenix, Arizona 85013, in conjunction with *The Western Journal of Medicine*. All views and opinions expressed in the articles published herein are the authors' and may or may not reflect those endorsed by the Arizona Medical Association.

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- Classified Advertising

From Our President

Joseph W. Hanss, Jr., M.D.

This is the last issue of *Arizona Medicine* in this format, that is, as a magazine insert in *The Western Journal of Medicine*. ArMA appreciates the long relationship we have shared as a participant in the Western Journal. We will miss many of its valued attractions. I personally wish to thank the Journal editors for their advice and support over the many years we have worked together, and to reassure them that our departure is driven only by our internal need to change our approach to communicating with our members.

In the month of August, your officers and representatives on ArMA's Board of Directors were asked to contact non-members and former members of ArMA to ask them to renew their commitment to organized medicine. The officers and Board members asked non-members to enter their names on ArMA's membership roll, to support our mutual interests with their dues, and to stand up to be counted, ***UNITED.***

I now ask each of you to look up your friends and colleagues in BOMEX's medical directory of licensed physicians. Search for the "M" (which indicates ArMA membership) following each friend's name. If it is missing, personally invite them to become members. ArMA's staff will assist you if necessary.

Remember, there's nothing like the personal touch.

Next month, ArMA will give birth to a new *Arizona Medicine*. It will be a monthly newspaper full of breaking news of importance to the medical community, information about ArMA's programs of benefit to members, commentaries from physicians around the state and point-counterpoint debates on the hottest issues in medicine.

Your officers and representatives in the House of Delegates hope this change in style, format and communications content will improve your ability to quickly identify and absorb facts and events which influence you and your practice of medicine.

ArMA exists for its members. ArMA's impact increases as it represents a larger and larger percentage of the practicing physicians in the state. ArMA's influence is also directly proportional to the degree that its membership understands the issues that confront medicine.

I intend to improve both the numbers and the awareness of our membership.

Joseph W. Hanss, Jr., M.D.

Having trouble finding your way to the right insurance company?

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MEDICAL MALPRACTICE

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The Medical Importance of Illiteracy

Recent evidence indicates that 10 percent of U.S. adults lack basic reading skills. This means that 15 million American adults cannot read the front page of a daily newspaper, a letter from their child's teacher, or the warning label on a can of poison. An additional 30 million Americans (estimates vary) are functionally illiterate, meaning that they do not possess the literacy skills necessary to fully participate in society as a family member, community member, citizen, consumer, job-holder, or member of social, religious or other organizations.

Illiteracy in the U.S. is most prevalent among persons of low socioeconomic status, and is a particular problem among low income single mothers and minority groups, among whom illiteracy rates may exceed 50 percent. Illiteracy is not limited to these groups, however. Illiteracy in the U.S. is present in all socioeconomic strata and in all geographic locations. Although large urban areas are often considered to have the highest rates of illiteracy, the problem is also common in rural areas, where high school completion rates are often below those in central cities.

Given the widespread prevalence of illiteracy, it is not surprising many patients cannot understand written health-related information. For example, up to half of patients presenting to some hospital emergency rooms are unable to comprehend standard written instructions provided to them upon discharge. Surgical consent forms and consent forms for research projects are often written at the graduate school level or higher. In addition, most educational handouts published by medical organizations are written at difficulty levels that exceed the reading ability of the average American (the average reading skill of adults in the U.S. is at the 8th grade level).

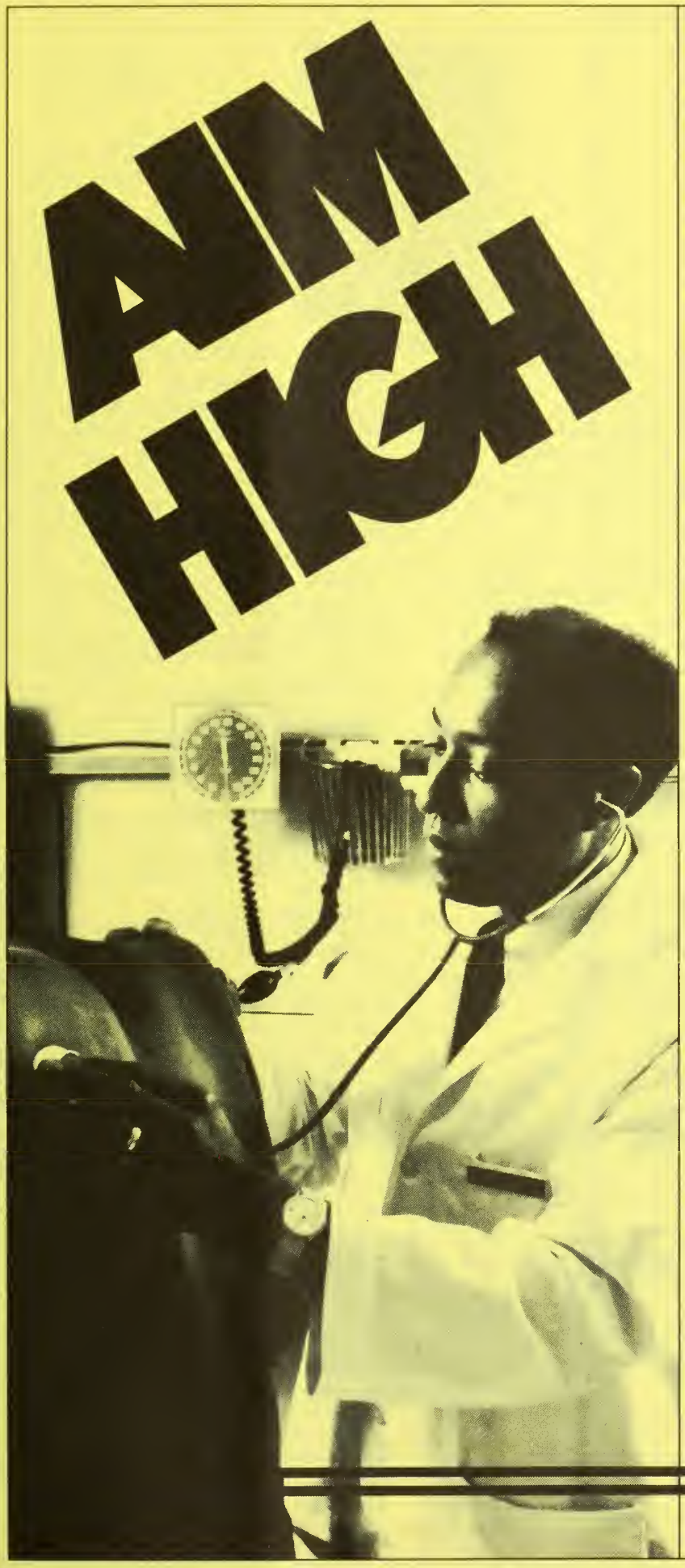
There are two important implications for health professionals. The first is medicolegal. What is the individual health provider's responsibility when a patient fails to understand important information provided in written form? Many experts believe that the public's "right to know" is not nullified by the public's inability to read. Significant information must be effectively explained, even to those who cannot read.

The other important implication is more wide-reaching; the public's health is dependent on the health care system's ability to provide the public with important preventive health information. But what percentage of the population was able to read, for example, the AIDS information brochure distributed to all American households by the surgeon general? And how many individuals are able to fully comprehend details of low cholesterol diets, considered so important for cardiovascular health, which are regularly published in newspapers, periodicals, and health information brochures?

The poor health status of illiterate individuals emphasizes the medical importance of illiteracy. Research recently completed at the University of Arizona College of Medicine demonstrates a strong, direct and independent association between literacy and physical health. Individuals with poor literacy tend to have poor health. This relationship persists even after controlling for variables such as age, ethnic background, income, employment status, and others.

Although the mechanism(s) by which illiteracy contributes to poor health is unclear, the lesson is still the same. Poor readers tend to be less healthy. Improving the health status of illiterate individuals will require providing them with health-related information in usable form. To do so, we must be able to impart that information with methods other than standard written communication. There must be an increased use of health education materials which are specifically designed for individuals with very low literacy skills (i.e., at or below the fifth grade level). There should also be a greater reliance on non-written methods of education such as models, audiovisual, and mass media techniques. ■

Barry D. Weiss, M.D.
Associate Professor
Chief, Section of Family Medicine
Department of Family and Community Medicine
University of Arizona College of Medicine



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To the Editor:

Jane M. Orient, M.D.

Recognizing the increasingly important contributions that bureaucrats make to medical care, the Association of American Physicians and Surgeons (AAPS) has established a prestigious new award. The first Bureaucrat of the Year will be honored at the 47th annual meeting of AAPS in Scottsdale, Arizona, on September 12, 1990.

Bureaucrats now perform functions that once required a physician's judgment, such as deciding how long patients need to be in the hospital, and whether they need to be in the hospital at all -- without even having to see them. Bureaucrats judge whether a patient's care has been appropriate or deviant. Then they decide how much a treatment is worth, and how much a doctor is allowed to charge for it.

The humble bureaucrat usually functions anonymously, quietly, behind the scenes, expecting no reward save his paycheck, his perks, and an occasional bonus for identifying an unusually large number of deviant doctors.

"It's time for these selfless, nameless, faceless public servants to receive their rightful share of public acclaim," stated AAPS Executive Director, Jane Orient, M.D.

The Bureaucrat of the Year will be chosen by a stringent method modeled on the procedures used by Peer Review Organizations (PROs) in sanctioning physicians. Reasons for nominations -- for example, an outstanding effort to implement Governor Lamm's mandate for preventing medicine (let them die and get out of the way) -- must be clearly documented. A single act, if sufficiently gross and flagrant, could merit the award, but generally a substantial number of acts should be detailed.

The names of the persons submitting nominations will be kept confidential, also following the precedent set by PROs, as well as the American tradition of equality before the law.

The chosen honoree will be hanged in effigy from the Liberty Tree, after a fair hearing.

The award follows a tradition begun in 1764 by the Sons of Liberty. Parliament had passed the Stamp Act, which required that all business and legal transactions be conducted on officially stamped paper. The colonists, enraged at this interference with commerce, rallied behind Sam Adams. They hanged an effigy of stamp

Continued on page 10

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Building Cathedrals: One Physician's Perspective

Michael T. Kovalchik, M.D., Director of Dialysis,
Charlotte Hungerford Hospital, Torrington.

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I awoke suddenly, unsure why, as I glanced through the penetrating darkness at the blinking readout of the alarm clock. 3:55 A.M. Suddenly the phone, and I realized why I was awake. "Yes, hello, Mr. Jenkins, cardiac arrest, I'll be right there." I stumbled to the bathroom with the legs of a drunk attempting to walk a straight line. A quick splash of the face, a comb through the hair, a fast change of clothes, and I was out the door. However, I was quite pleased when I remembered to call the answering service to inform them of my return to the hospital so my wife would not be plagued by the incessant telephone.

On the way to the hospital, I observed a beautiful moonlit night with fresh soft snow, untouched and velvet. The quiet was so intense I could feel it. I recalled Mr. Jenkins, an associate's patient, whom I had cared for on several prior occasions. A simple but honest man whose heart was ravaged by virtually totally occluded coronary arteries. He was a farmer who lived off and loved the land. He was surrounded by a caring and devoted family. His children all lived on land he provided near his farm. They had supported him in the last two years while everyone predicted he would not survive. Home oxygen, intramuscular morphine, and love.

I left the family with their grief. They were soon to live their own personal soap opera. I had to put it behind me, but I knew it was not possible.

As I walked into his ICU room, he was surrounded by a swarm of white uniforms, counting, measuring, documenting the progress of the resuscitation. The focus was on recording, skillfully avoiding the drama of a life hanging by a thread, dependent on the events at hand. I paused, and everyone stopped and waited for me to take charge. I waited, observed his face, and knew the situation was hopeless. Codes, once started, tend to develop their own momentum no matter how impractical, hopeless, or simply futile they may seem. We tried everything and I performed my duties almost ritualistically. After nearly one hour, I, like the maestro, pronounced that we had completed our symphony and proclaimed the mechanical last rites to be complete. Everyone sighed and quickly left the room, leaving me alone with Mr. Jenkins. I could hear small talk among the staff through the closed curtain as I paused to observe him. His body was all that was left of this extremely vital man. Why was it that his family loved him so? I could imagine him as an infant, a child, a young man stealing his first kiss from his future wife. I could picture his enthusiasm as a new father, holding his fragile baby son with his rough calloused hands. He was gone. What happens to all his experiences, enthusiasm, and the meaning he worked so hard to touch?

I slowly walked out of the ICU, making my way to the waiting room. The family was there, crowded together, anxiously awaiting my entrance. Did they know he had perished? The look on their faces mirrored hope, anxiety, and tension, so intense it was physically apparent. I sat down, an empty chair was waiting, sighed, and announced he was gone. The scene that followed was one I had witnessed so many times before. Physical anguish, verbal sorrow and loss, all converged. The intensity was incredible. The room shrank upon me, the temperature rose while I waited. Time seemed to stand still. I had learned to wait. Nothing can contain these emotions. To interject at this juncture, to attempt to negate the grief as I have so often observed only masks the physician's sense of frustration, anxiety, and inability to touch his own feelings. I remember Shakespeare (Macbeth, Act IV):

"Give sorrow words: the grief that does not whispers the o'er-fraught heart, and bids it break."

After what seemed like countless minutes, there was a pause and I finally spoke. I explained the circumstances surrounding his death and concluded that in the end he did not suffer. I looked at all their eyes. Each pair spoke to me with incredible emotion. Each set was colored differently by their own unique experience. An expectant mother, a new father, a brother. Was he next? Had Mr. Jenkins rocked his now pregnant daughter to sleep in an old wooden cradle when she was a tiny infant?

I left the family with their grief. They were soon to live their own personal soap opera. I had to put it behind me, but I knew it was not possible. To deny these feelings was impossible for me. I just had to tuck them into a corner with the rest of my experiences.

Morning! I felt the loss of my daily shower as I made my rounds in ICU. I sipped my coffee as I reviewed the hearts of my three remaining patients. I started my rounds. Mr. Giovanni, a wonderful man, kind, gentle, was slowly drowning in his pulmonary edema. He had a severe cardiomyopathy coupled with renal failure requiring dialysis. However, dialysis could not keep up with the failing heart. Fluid kept coming back. He suffered so in his breathlessness. He smiled as I entered, a smile that exuded compassion and kindness. He asked little. Finally I asked if there was anything I could do for him. He said no, again with a smile. I left, sensing his pain and suffering, but mostly uplifted by his courage. Could he pull through?

I drifted over to Mr. Pont, a mentally retarded man, on a ventilator due to an unknown pulmonary process with early kidney failure and severe ischemic heart disease. He had been in the ICU for weeks. His prognosis was hopeless. Unfortunately, he was a ward of the state. His distant family, while caring for him, felt powerless in making those decisions at the end of life. Who was responsible? Could we make him a DNR? Could we withdraw the ventilator? Physicians, family, and administration, where did we fit? Who would take the responsibility? Finally, out of frustration, I wrote DNR. As a physician, I deemed the situation hopeless., I felt no obligation to prescribe therapy, I felt ineffective. Would the state challenge me or threaten the hospital accreditation if we did not attempt resuscitation? To me, this was a final episode of a long chapter. I had experienced this similar situation too many times and felt powerless. It was time to recognize my value system and act accordingly.

I slowly walked to the third patient, Mrs. Godburn, brought to the emergency room from the nursing home. The family had carefully thought out their desire to avoid heroic life-saving measures in this 86-year-old woman who had suffered several strokes, was totally bedridden, and did not recognize her family while requiring feeding through a gastric tube. A "no code" was dutifully written on her chart in the nursing home. When she stopped breathing, the nurse, her first day on the job, called the paramedics without consulting the chart. When they arrived, they were informed of the "no code" status. However, they proceeded to perform CPR. "State policy," they could not still their own momentum once called regardless of the patient's or family's wishes. So there she was on the ventilator with a very angry family at her side. I was left to attempt to pull the pieces together. I had no energy left. I recalled the origin of the term "scapegoat" and understood that the family had just given me all their guilt and anger. I took it with me as I left the room.

It was late and I was moving slowly. Nine more hospital patients to see before the afternoon patients started. Two of these patients were awaiting lengthy discharge instructions. I made a quick inventory of my options. I cancelled my noon administrative meeting and cut a few corners making rounds. I often toyed with the fantasy of not answering my incessant pages. I could not put off any office patients as there was no way to reschedule them in the next few weeks. More importantly, I always felt uncomfortable cancelling patients' appointments; it only prolonged their anxiety and intensified my work load.

I proceeded with my rounds and discharges. I thought of my children who again found their father gone when they awoke. My wife, in some ways, a married single parent coping with the uncertainty of my schedule and the threat of the telephone.

I recalled that my first scheduled patient in the afternoon was to be a young woman with a strong family history of polycystic kidney disease. She had elected not to undergo screening over the years. She had observed her mother's experience with dialysis and transplantation. Every complication possible had occurred and her mother died a very undignified death. I knew this had to weigh heavily on her mind as she waited to see me. She was soon to become a bride and as a consequence requested screening. Unknown to her, the ultrasound performed one week earlier was positive.

The fatigue, frustration, time urgency, and bureaucratic roadblocks weighed heavily on me. I had to collect myself as I moved from patient to patient. My patients were unaware of my day's experience. I had to let go of all the day's conditioning in order to connect with them. If I brought with me all the baggage from the early morning, I would be of no use to them. If I was to find a common language between myself and the patient, I had to be open and disconnected from everything except what was happening with that particular patient.

I left the hospital and made my way to the office. I recalled the old story of a man who visited a quarry, observing many men all doing the same thing, dressing stones. He approached one and asked him what he was doing. The stone cutter replied, "Making a living." He then approached another worker and asked the same question. This time the response was, "I am cutting stones." The third worker was approached and replied, "I am building a cathedral." All these men were doing exactly the same thing, yet each viewed what they were doing differently. The first viewed himself only in terms of his immediate desire, the second in terms of the technical challenge, whereas the last man incorporated the needs of the other workers but went beyond. So, when physicians, regardless of their accomplishments, view their work simply as fulfilling their immediate desire or as a technical challenge, they will only be making a living. I knew as I walked into my consulting room I was about to participate in an experience that was likely to be unique and long-remembered by the patient. How I conducted myself would influence to a great extent how the young woman would cope with the newly acquired diagnosis. As I walked in, she was standing reading a quote from Longcope on my consulting room wall.

I knew this had to weigh heavily on her mind as she waited to see me. She was soon to become a bride and as a consequence requested screening.

Pope has said that the "proper study of mankind is man" and even though a clinician has science, art, and craftsmanship, unless he is intensely interested in human beings, he is not likely to be a good doctor.

We shook hands and I closed the door. All of the fatigue, the events of the day, the cacophony of pages faded behind me. The unique bond of a physician/patient relationship energized me. I, newly vitalized, attempted to transcend my rudimentary obligations and focus on the unique magnitude of the task ahead. ■

Who's Going to Look Out For Me?

(Continued from page 1)

Someone needs to pay attention to what is happening to these physicians. Unfortunately, the strains have lead some to become severely depressed and seek solace with mind-altering substances. Others have been unable to even find a way to deal with the situation and have sought relief in other more extreme ways. This is a problem not only for our profession, but also for our society. They need to help us deal with these changes since many are occurring at a higher level than our profession alone. Calls for retribution of impaired physicians will only accentuate the problem and make it more difficult to treat. Since the vast bulk of physicians currently practicing in the United States fall within this age group, I suspect more fallout will occur unless a determined effort is made, both by ourselves and others, to begin thinking, like my father, of our own existence. ■

Marshall B. Block, M.D.
Editor

LETTER TO THE EDITOR

(Continued from page 7)

master Andrew Oliver from the Liberty Tree next to a large boot, symbol of the hated Lord Bute, author of tax legislation designed to support a network of British mercantilist regulators.

In 1764, the award was highly controversial. Benjamin Franklin felt that defying the Stamp Act was like trying to hinder the setting of the sun. Working within the system, he proceeded to get his relatives and friends appointed as stamp masters. William Tryon, Governor of North Carolina, although personally opposed to the Stamp Act, advised submission to the tax while he appealed to King George for special favors for his own colony.

Today, some physicians, like Ben Franklin, advocate cooperation with bureaucratic intrusions into the practice of medicine, in order to "make the system work better." They negotiate for advantages for their specialty, and may actually advise their fellow physicians to become bureaucrats themselves. (Such physicians are also eligible, perhaps even favored, to receive the award.)

An official ballot and further information about the awards ceremony are available from AAPS, 1601 N. Tucson Blvd., Suite 9, Tucson, AZ 85716. Please enclose a self-addressed, stamped envelope. Nonphysicians, as long as they have been or might sometime become patients, are also welcome to submit nominations.

Competition for the honor is expected to be fierce, and it may be necessary to confer it more frequently. As Herbert Hoover said, "I need the authority to hang a bureaucrat at least once a month, to serve as an example to the others." ■

Jane M. Orient, M.D.
Executive Director, AAPS

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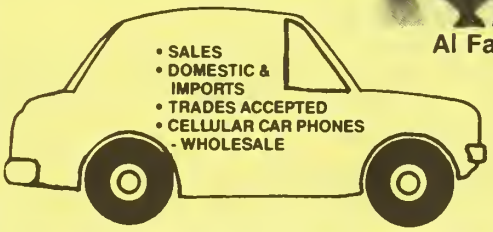

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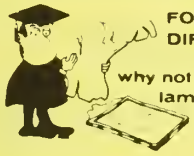

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ences of these various forms of ferritin have been demonstrated. Ferritin is also found in plasma, where its concentration tends to correlate with overall iron stores, despite the fact that most circulating ferritin is in the glycosylated form with low iron content. Normally about two thirds of storage iron is in ferritin, the synthesis of which is enhanced by an increase in iron stores.[11]

Hemosiderin, the poorly soluble aggregated form of tissue "stainable iron," probably represents the product of lysosomal degradation of tissue ferritin. It normally represents about one third of storage iron but is that form in which iron most markedly increases in iron overload syndromes. Hemosiderin iron can also be mobilized, through mechanisms that are unclear, for reutilization.

TABLE 1.—*Iron-Containing Compounds in Humans**

	mg in a 75 kg male (approximate)	*mg/kg (approximate)*
Functional compounds		
Hemoglobin	2,300	31
Myoglobin	320	4
Heme enzymes	80	1
Nonheme enzymes	100	1
	2,800	
Storage complexes		
Ferritin	700	9
Hemosiderin	300	4
	1,000	13
Total	3,800	50

*From Bothwell TH, Charlton RW, Motulsky A: Hemochromatosis. *In* Scriver CR, et al (Eds): The Metabolic Basis of Inherited Disease. 6th ed. New York, McGraw-Hill, 1989, p 1433.

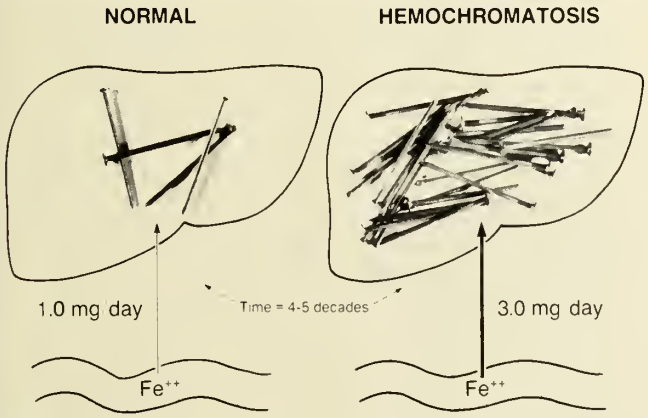

Figure 1.—Schematic illustration of the excessive absorption and storage of iron in hemochromatosis.

Transferrin, a specialized transport protein for iron, is largely synthesized in the liver and circulates in plasma with a half-life of about 8 days. This 77,000 dalton protein, which has two distinct binding domains for ferric molecules, is normally present in a concentration that can bind at saturation approximately 300 to 350 μg of iron per deciliter of plasma. It is normally about one third saturated with iron (ranges, 20% to 50% saturated). Transferrin is increased in concentration in the plasma and extracellular fluids during iron deficiency and decreased during iron overload. Normally only 4 to 5 mg of iron is found bound to transferrin.

Transferrin receptor.[12] Diferric transferrin molecules interact with specific cell surface receptors and are then internalized into the cell by receptor-mediated endocytosis (Figure 2). After the iron is released in the endocytic vesicle, both the receptor and the apotransferrin are recycled to the cell surface and become available for further use. The synthesis of the transferrin receptor is normally suppressed during iron loading and increased during iron deficiency, as might be anticipated teleologically.

Ferrokinetics (Figure 3). The body's iron does not exist in a homogeneous pool; it is found in various storage and functional forms. Nevertheless, all of it is ultimately available for mobilization and use. The shuttle movement of iron among cells and tissues, largely involving transferrin, is estimated at 25 to 35 mg per day in the average-sized adult. Ferritin and possibly other proteins may also serve to transport iron, in addition to the role played by transferrin.[13] This comparatively large internal circulation of iron is to be compared with a net input and loss of about 1.0 mg per day.

Absorption of Dietary Iron (Figure 4)

This brief review of hemochromatosis does not allow for an extensive discussion of the absorption of iron from the diet.[10] In general, two factors are paramount in controlling the amount of iron that is absorbed: (1) the amount and the bioavailability of iron in the diet and (2) the transport "set" of the intestinal mucosa.

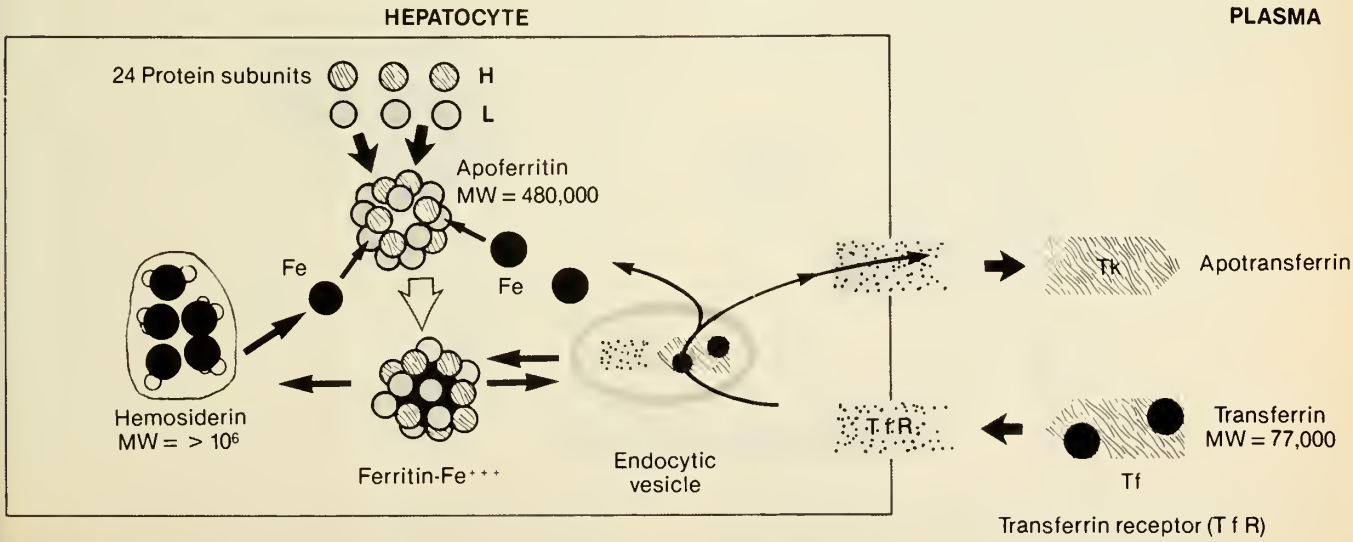

Figure 2.—The transport, storage, and use of iron in the body as illustrated by the hepatocyte. MW, molecular weight.

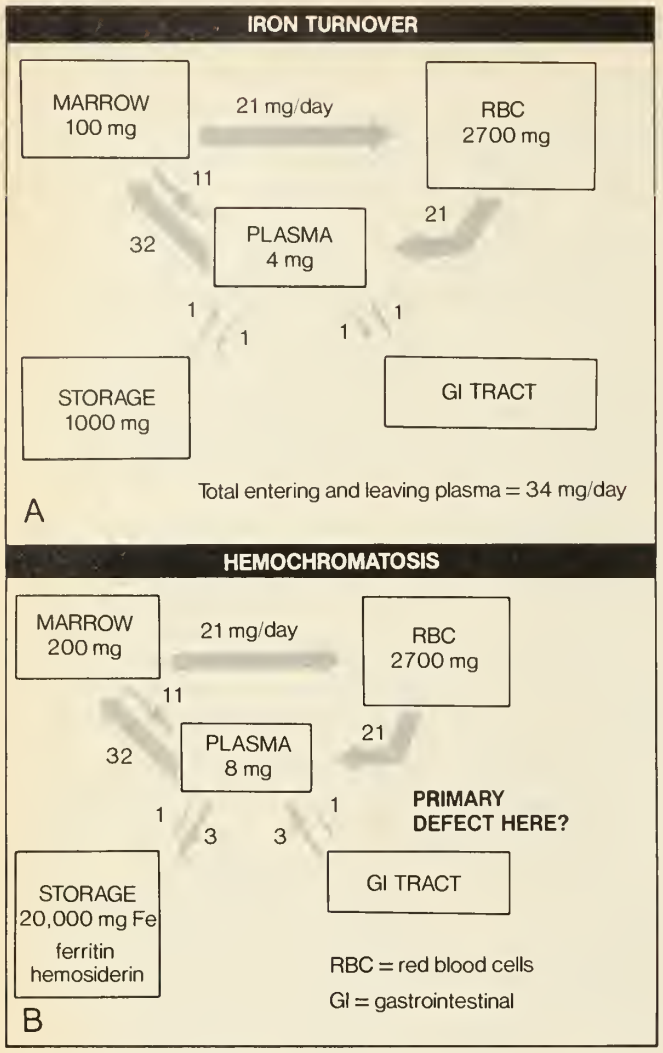

Figure 3.—**A,** Iron pools and turnover in normal humans; **B,** Iron pools and turnover in hemochromatosis.

Dietary Iron. The average American diet contains about 6 mg of iron per 1,000 kcal, or about 12 to 20 mg of iron per day. Of this approximately 90% is "free" iron and 10% is bound in heme. Heme iron is much more readily absorbed (~25%) as the intact molecule with subsequent intracellular release of iron by heme oxygenase. Nonheme iron is more poorly absorbed (~3%), presumably because of inhibition by certain ligands and other factors. Ascorbic acid greatly improves the absorption of nonheme iron both by reducing it to its more readily absorbed ferrous form and also by binding to it directly. Intraluminal factors seem not to play a primary role in the pathophysiology of hemochromatosis, so they will not be discussed further here.

Mucosal Transport. Normally there is a loss of only about 1.0 mg of iron from the body a day, largely through desquamation of cells and the loss of a small amount of blood.[1,10] This loss may be doubled in women through the blood loss of menstruation and the iron loss of pregnancy (approximately 500 mg). *There is no effective physiologic mechanism for the body to control iron balance through alteration of excretion if absorption is deranged.* This is unique for iron among the body's inorganic components, cations or anions. Homeostasis therefore requires a tightly controlled mechanism for the active absorption, or exclusion, of iron by the intestinal mucosa.

The components of the mucosal cell's mechanism for selective absorption of iron are unclear.[14,15] Included must be mechanisms for uptake of both heme and nonheme iron from the lumen, transport within the cell, possibly storage and sequestration within the cell, and release into the body for transfer elsewhere, largely as transferrin (Figure 4). The apoferritin/ferritin system has been a central focus of attention for many years as a potential controlling device for storage or transport of iron within the mucosal cell. Despite the work of many investigators, such an additional monitoring role for this specialized iron storage protein has not been established. In atransferrinemia the absorption of iron is enhanced rather than reduced.[13]

The "set" of the mucosal absorption of iron seems to

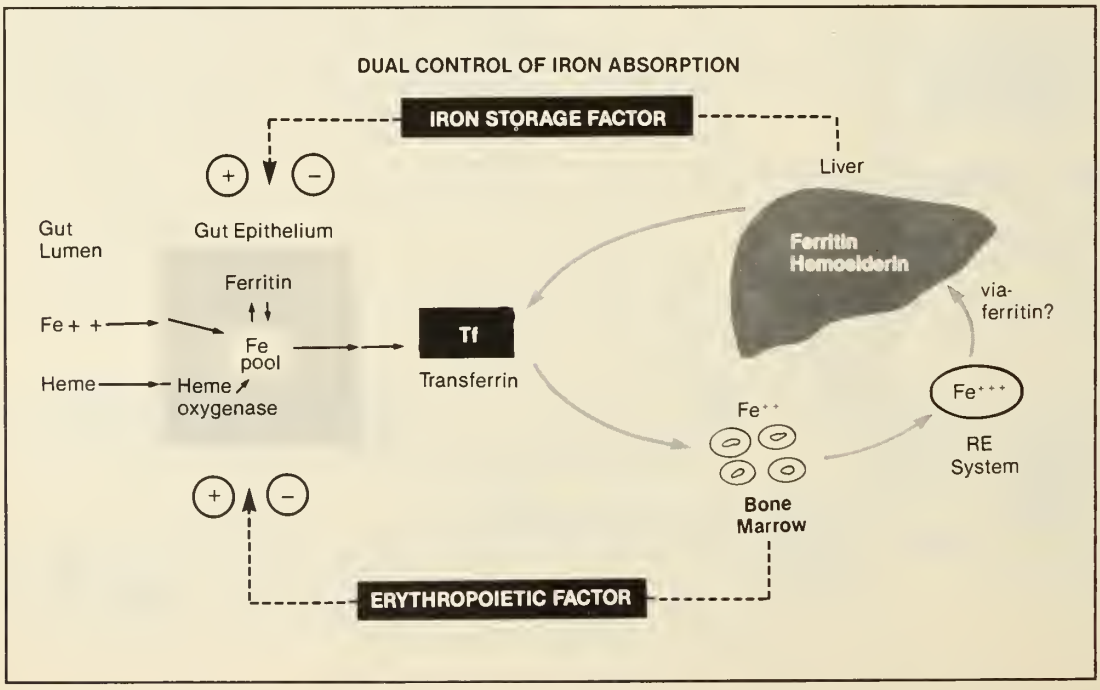

Figure 4.—A simplified illustration of the two physiologic variables that control iron absorption. The molecular details of the mechanism of iron transport control by the intestinal epithelium and the nature of the feedback signals remain to be elucidated.

depend on at least two independent variables[1,10] (Figure 4):

1. The state of iron stores. There is a very close adaptation of the absorption of iron to the amount of storage iron. Iron deficiency enhances absorption; iron excess depresses absorption. How the mucosal cell senses the state of the iron stores is unclear. Is it a local adaptation based on iron stores within the cell itself or does it receive a hormonal signal or some other type of signal from elsewhere?
2. The rate of erythropoiesis. An abnormally high rate of erythropoiesis will enhance iron absorption even in the presence of iron stores. This has been particularly noted in syndromes with ineffective erythropoiesis, such as that found in the thalassemic syndromes or in some of the sideroblastic anemias. This stimulus to iron absorption, presumably originating in the bone marrow, obviously requires a distal signal to the intestinal mucosa, but what that signal might be has not been established.

In brief, the control of the absorption of iron by the mucosal cell is the principal mechanism for maintaining a normal balance of iron. Two seemingly independent variables control the "set" of the mucosal cell: the state of iron stores and the rate of erythropoiesis. The cell biology of how absorption is appropriately adjusted by the intestinal mucosa and the nature of the signal or signals that it receives have not yet been clarified.

Pathophysiology of Hemochromatosis

Hemochromatosis is characterized by a loss of rate control resulting in a continued inappropriate absorption of dietary iron in the face of a pathologically enlarged store of iron. Both heme and nonheme iron seem to be absorbed excessively.[15] The rate of iron absorption may be reduced to normal as storage iron expands, but it remains inappropriately high for the level of storage iron attained. The excessive absorption is usually in the range of 1 to 3 mg of iron per day, leading to a total pool of 15 to 35 grams of iron over 35 to 60 years (see Figure 1).

The derangement leading to this abnormal avidity for iron remains obscure. Ferrokinetics are normal in hemochromatosis, except for the higher level of circulating iron (see Figure 3). No consistent abnormality of transferrin or its receptor has been found, and the genes for both are on chromosome 3 rather than chromosome 6, where the gene for hemochromatosis is found. Similarly, no abnormality of any of the isomeric forms of ferritin has been consistently found. The ratio of H to L subunits of intestinal ferritin was found to be normal, although the total level of ferritin was lower than would be predicted from the levels of plasma ferritin.[15] As already noted, the ferritins are not attractive candidates for the abnormal gene product of hemochromatosis because their coding genes are not on chromosome 6. The reticuloendothelial system seems to be relatively spared in hemochromatosis, with the major deposition of iron appearing in parenchymal cells, in contrast to what is typical in other iron overload syndromes.[9] Although this may be simply the result of the very slow accretion of iron over decades, attempts have been made to document abnormalities in iron metabolism in cells other than mucosal cells. An increase in the release of ferritin by monocytes from hemochromatotic patients has been recently described,[16] but this awaits confirmation.

In brief, although the general pathophysiology of hemochromatosis is clear, the specific abnormal gene product is not yet known. It is possible that elucidation of the abnormality may become apparent first through "reverse genetics," i.e., through isolating the abnormal gene prior to identifying its product, as was the case for Duchenne muscular dystrophy.[17]

Genetics of Hemochromatosis

The demonstration in 1975, since widely confirmed, that hemochromatosis is closely linked to HLA-A3 has led to major progress in understanding the disease[8,18] and may ultimately lead to isolation of the gene at fault (Table 2). In brief review, the gene for hemochromatosis is believed to be in close physical proximity to the HLA complex on the short arm of chromosome 6, probably found between the HLA-A and HLA-B loci and within 1,100 to 1,600 kb of HLA-A. This tight linkage to HLA leads to a recombination rate of only about 0.01. In addition to the linkage disequilibrium with HLA-A3, associations have also been noted with HLA-B7, HLA-B14, and HLA-A11. The reason for this tight linkage with HLA-A is unclear; it is probably due to the fortuitous location of a wholly unrelated gene. It has been postulated that the linkage of hemochromatosis to certain haplotypes of HLA-A and HLA-B could be caused by an initial rate mutation, presumably in an A3, B7 founder, followed by various chromosomal recombinations, one of the earliest of which led to A3, B14. The sequence of other chromosomal recombinations together with population migrations might have then led to the dispersal of the gene for hemochromatosis and its linkage that we find today.[18]

Some of the practical aspects of the discovery of the HLA linkage of hemochromatosis are as follows:

1. This has allowed the clear demonstration of the genetic nature of the disease and its autosomal recessive transmission (Figure 5).
2. Within families it has allowed the definitive diagnosis of homozygotes and heterozygotes and therefore the opportunity for early therapeutic intervention (Figure 5).
3. It has clarified "pseudodominant transmission" of the disease as being the result of the mating of a homozygous and a heterozygous parent.

TABLE 2.—*Linkage Disequilibrium Between Hemochromatosis and HLA**

HLA	*Hemochromatosis*	*Controls*
A3	73%	20-30%
B7	46%	20-25%
B14	20%	6-9%

*Data from Simon M et al: The genetics of human chromatosis. Prog Med Genetics 1980; 4:135

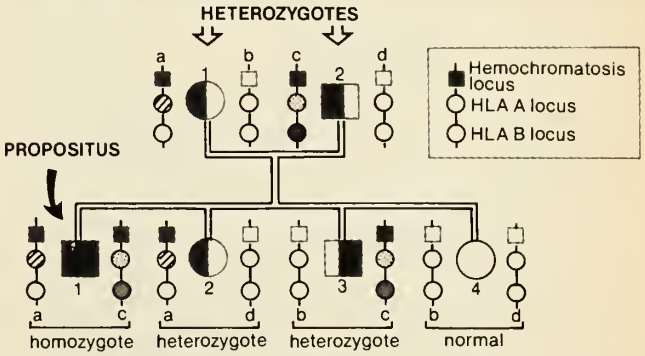

Figure 5.—Linkage of hemochromatosis alleles with HLA haplotypes in a family with a precise mendelian distribution. The relationships between the gene and the A and B loci are shown as topographic approximations. (Reprinted by permission of Beaumont CM, Simon M, Fauchet R, et al: Serum ferritin as a possible marker of the hemochromatosis allele. N Engl J Med 1979; 301:169.)

4. It may well allow for isolation of the abnormal gene and the determination of the true phenotypic nature of hemochromatosis rather than its indirect study as reflected in aberrant iron metabolism.

HLA typing is of no practical use in surveying for hemochromatosis in the population at large. Neither is it of use in the diagnosis of an individual patient if the particular linkage of HLA and hemochromatosis has not been established in at least one member of that family by the independent means of demonstrating iron overload.

Prevalence of Hemochromatosis

In the absence of a direct marker for the disease, the prevalence of hemochromatosis can be approximated only by large surveys for the detection of iron overload. Iron overload is presumed to represent hemochromatosis in the absence of other known causes, such as excessive ingestion of iron, transfusions, increased erythropoiesis, and other possible diagnoses to be discussed later. When an index case is identified, other cases of hemochromatosis can be identified by family studies based on haplotype and allele sharing.

A large number of such studies, carried out in many parts of the world, have demonstrated reasonably consistent findings for individuals of European origin.[19,20] First, the gene frequency for hemochromatosis is approximately 0.05; i.e., approximately 10% of whites carry one gene for hemochromatosis and are therefore heterozygotes. Second, approximately 1 in every 300 to 400 individuals is homozygous for hemochromatosis. (Recent Swedish studies suggest that the figure may be closer to one in every 1,000 persons.[20]) This means that possibly 500,000 to 700,000 persons in the US have hemochromatosis, allowing for presumed ethnic differences in population. Hemochromatosis may therefore be the most prevalent genetic disease of whites, roughly comparable to the prevalence of sickle cell disease in blacks. The prevalence of hemochromatosis in nonwhites seems to be much less, but this finding has not yet been well studied. These surprising conclusions have raised the following questions:

1. Why would a recessive disorder such as hemochromatosis continue at such a high prevalence? Is there some countervailing advantage to being a carrier of hemochromatosis, comparable to the protective effect of sickle cell trait against falciparum malaria? Is it possible that the increased ability to absorb iron exhibited by the heterozygote may have had some selective advantage? Is it alternatively possible that the HLA-A3 haplotype has carried some selective advantage and that the hemochromatosis gene has been the passive beneficiary through chance propinquity? Hemochromatosis carries very little reproductive disadvantage, since its major manifestations usually occur after the time of most active reproductive function.
2. Why is hemochromatosis so rarely diagnosed if 1 out of every 300 to 400 patients who enter our hospitals and clinics has this disease? This conundrum will be discussed subsequently.

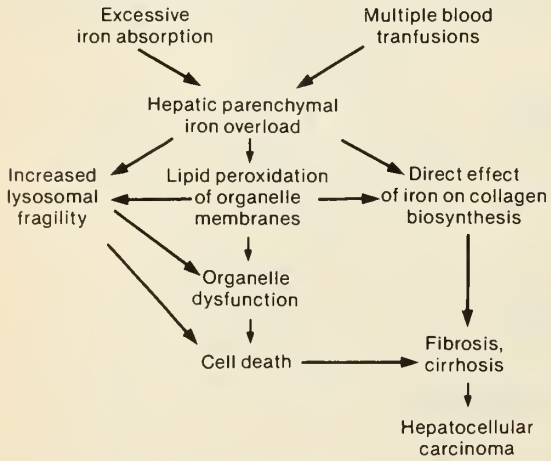

Figure 6.—Proposed pathophysiologic mechanisms of liver injury in chronic iron overload. (From Bacon BR, Brittenham GM, Park CH, et al: Lipid peroxidation in experimental hemochromatosis. Ann NY Acad Sci 1988; 526:155.)

Mechanisms of Tissue Damage in Iron Overload

The exact mechanisms by which chronic iron overload leads to tissue injury and fibrosis are not established. The current leading theories are reflected in Figure 6. Iron overload results in peroxidation of cellular lipids both in vitro and in vivo, either through the formation of oxygen-free radicals or through the formation of ferrous-dioxygen-ferric chelate complexes.[21] Peroxidation of lipids injures lysosomal membranes with the intracellular release of hydrolytic enzymes and impairs hepatic mitochondrial oxidative metabolism.[22] Hepatic microsomal function is also impaired in experimental iron overload, as reflected in a decrease in cytochrome P-450 concentration and aminopyrine demethylase activity. Excess hepatic iron may also directly increase the synthesis of collagen in the liver independently of producing necrosis of hepatocytes. Excess iron increases the catabolism of ascorbic acid and may lead to scurvy when dietary sources of that vitamin are marginal.

Clinical Manifestations of Hemochromatosis

Variables in the Clinical Expression of Hemochromatosis

As a genetic disorder, hemochromatosis is present from birth. Insofar as is known, however, the only adverse effect of the abnormal (or missing) gene product is that of continued excessive absorption of iron and its excessive storage in parenchymal cells. No definitive abnormality in the body's internal economy of iron usage and exchange has been found other than its excessive storage. Typically, hemochromatosis becomes clinically manifest in later life, in men more frequently than women (9–10:1), and in the presence of expansion of the body's storage iron by 20- to 30-fold. At least five variables influence the age of onset and the severity of the manifestations of the disease.

1. *Time.* As previously noted, the extra absorption of iron in hemochromatosis is usually in the range of 1 to 3 mg per day. Because of this slow accretion, the 15 to 35 grams of storage iron characteristic of the disease usually accumulate over decades, with the clinical manifestations of the disease most commonly appearing in the 5th and 6th decades.[6,7]

2. *Dietary availability of iron.* The rate of iron absorption in hemochromatosis is influenced by the amount of dietary iron and by other variables that normally affect iron absorption, such as ingestion of ascorbic acid, action of intraluminal ligands, mix of heme and nonheme iron, and other factors.[10]

3. *Loss of iron.* For practical purposes, this means the loss of blood. Hemochromatosis is an autosomal disorder, occurring equally in men and women. The clinical manifestations of the disease are found much more rarely in women, however, who represent only about 10% of reported cases. This has been attributed to the extra loss of iron in women through menstruation and pregnancies; however, other factors may be at play, including lower levels of dietary iron.

4. *Genetic heterogeneity.* Hemochromatosis may present with severe iron overload during childhood or, conversely, may produce no clinical abnormalities throughout the life of the patient. As is the case for other genetic disorders, it can be assumed that a number of different mutations at the hemochromatotic locus may impair the function of the gene product to varying degrees and in this manner contribute to the variable phenotypic severity of the disease.

5. *Specific organ involement.* The pattern of organ damage in hemochromatosis does not follow a predictable sequence. The causes of these variations are unknown.

Frequency of Clinical Manifestations of Hemochromatosis in Homozygotes and Heterozygotes

As noted, the use of HLA linkage studies within families permits the diagnosis of homozygous and heterozygous hemochromatosis independent of studies of iron metabolism. This has allowed for estimations of the frequency with which abnormalities of iron metabolism and clinical manifestations of iron overload occur in the presence of the abnormal gene or genes.[23,24] In these studies adult heterozygotes were found not to develop the clinical manifestions of hemochromatosis, but approximately one third of them exhibited evidence of minor iron overload (somewhat increased transferrin saturation, increase of hepatic iron by stain and analysis). All adult male homozygotes exhibited major iron overload, and some clinical manifestations attributable to hemochromatosis were present in 11 of the 13 studied (85%). All female homozygotes also exhibited some iron overload but less than that of their male counterparts (average body iron of about 8 grams as opposed to 20 grams for men). Only one of the seven women studied had clinical manifestations of hemochromatosis.

This small series is consistent with previous observations of the increased frequency of the clinical manifestations of hemochromatosis in men and the greater iron overload in men as an explanation of that fact.

Symptoms and Signs of Hemochromatosis (Figure 7)

Patients may exhibit a wide variety of symptoms and signs at the time of initial presentation.[1-3] Many of these are nonspecific or may suggest other disorders. The classical manifestations of hemochromatosis (the triad of cirrhosis, diabetes mellitus, and pigmentation) are late complications and occur together in a minority of patients. In view of its high prevalence, hemochromatosis must be considered more frequently in the presence of presentations such as atypical arthritis, impotence, cardiomyopathy, and upper abdominal pain. The clinical abnormalities of hemochromatosis will be discussed for convenience under the various organ systems involved. As noted, however, the mix of organ dysfunction may vary widely among individual patients for reasons that are unclear.

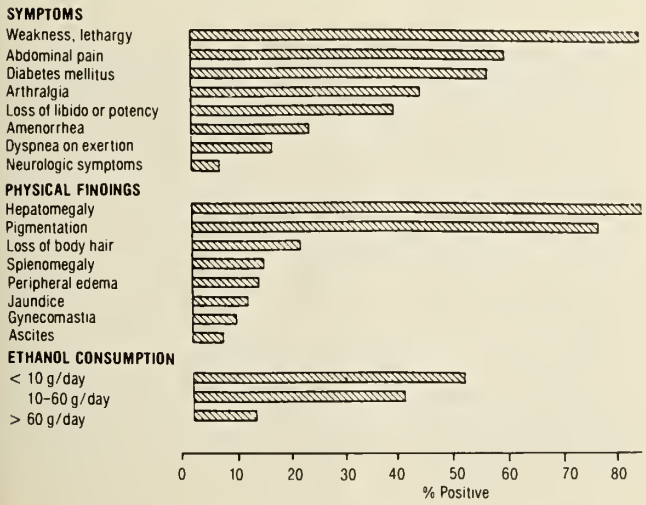

Figure 7.—Frequency of clinical symptoms and signs at the time of diagnosis in 163 patients with hemochromatosis. (From Bothwell TH, Charlton RW, Motulsky A: Hemochromatosis. *In* Scriver CR, et al (Eds): The Metabolic Basis of Inherited Disease. 6th ed. New York, McGraw-Hill, 1989, p 1433.)

Liver. The liver is normally a major site of iron storage. It is not surprising, therefore, that it is often pathologically and clinically involved in hemochromatosis.[7,10] In fact, measurement of the concentration of iron in the liver is the most definitive test for the diagnosis of an index case of hemochromatosis. Levels may exceed the normal level of 40 to 120 μg of iron per 100 mg dry weight by 50- to 100-fold. Typically, hemosiderin granules are seen as stainable iron, particularly in hepatocytes and in bile duct epithelium. Iron is rarely seen in the Kupffer cells until the later states of the disease, in contrast to the iron overload seen in secondary hemochromatosis, such as that occurring after multiple transfusions.[9] Accompanying the iron deposition, degeneration of hepatocytes and varying degrees of fibrosis are seen. In advanced hemochromatotic liver disease there is hepatomegaly with macronodular cirrhosis. The classification of the initial histologic findings in a series of 71 cases is shown in Figure 8.[25]

The clinical manifestations of liver disease in hemochromatosis tend to be subtle and insidious in onset. Synthetic function is usually well maintained (albumin, prothrombin) and esophageal varices and ascites are less frequently present than in Laennec's cirrhosis. Three aspects of hemochromatotic liver disease are worthy of note:

1. The frequent association of clinical hemochromatosis and alcohol abuse has long been noted. Advanced cirrhosis may occur in hemochromatosis in the absence of alcohol ingestion, however. Patients with hemochromatosis who drink alcohol actually tend to have lower rather than higher levels of hepatic iron,[26] presumably due to a poorer diet, bleeding from gastritis, and other factors. It seems likely, therefore, that alcohol is an inde-

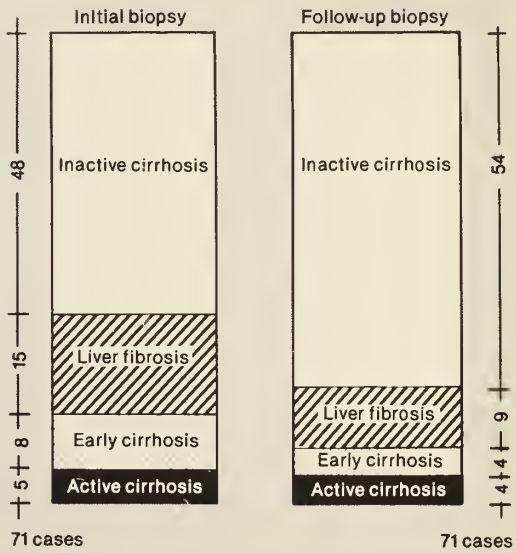

Figure 8.—Classification of initial histologic findings and follow-up findings in liver biopsies from a 71-case series. (From Tiniakos G, Williams R: Cirrhotic process, liver cell carcinoma and extrahepatic tumors in idiopathic hemochromatosis. Appl Pathol 1988; 6:128.)

pendent hepatotoxin in hemochromatosis, although it may add to the injury attributable to iron storage disease.

2. Hepatic function often improves markedly following the removal of excess iron by repeated phlebotomy. Actual reversal of fibrosis has been described, but this may be due to biopsy sampling errors. In a careful follow-up study of 71 patients during an average of 7 years of therapy, the histologic changes were classified as follows: unchanged, 62%; worse, 32%; improved, 5%.[25]
3. Hepatoma is a frequent complication of hemochromatosis, occurring in as many as 15% to 20% of those patients who have developed cirrhosis.[27] The increased risk of hepatoma in hemochromatosis is estimated to be 200-fold. Unfortunately, the successful removal of the excess hepatic iron by phlebotomy does not seem to reduce the risk of subsequent hepatoma.

As will be noted below, the development of hepatic cirrhosis adversely affects the long-term prognosis of patients with hemochromatosis.

Pancreas. The association of hemochromatosis with diabetes mellitus was noted early.[28] It remains, however, as a complex relationship. The reported prevalence of diabetes mellitus in hemochromatosis has varied widely depending on the stage of the disease at which the diagnosis was made. A figure of 40% to 60% of overt diabetes mellitus in hemochromatosis is most frequently reported.[2,7] Most pancreatic iron in hemochromatosis is deposited in acinar cells, but no exocrine deficiency of the pancreas has been described. In the islets iron is selectively deposited in the B cells, with no abnormalities of the islet cells A, D, and PP cells.[29] The islets are similar in iron overload of either genetic or secondary origin and differ markedly in structure from those found in either type I or type II diabetes mellitus. In hemochromatotic diabetes the insulin response to a glucose load is significantly impaired, but the secretion of glucagon is normal. An additional factor appears to be a degree of insulin resistance. Even in the presence of a normal glucose tolerance test, patients with hemochromatosis demonstrate a tendency toward insulin resistance as reflected in an inappropriately elevated level of plasma insulin.[30]

Patients with hemochromatosis and diabetes are subject to all the degenerative complications associated with diabetes, consistent with the duration and severity of the altered carbohydrate metabolism. With removal of iron by phlebotomy, as many as one third of patients exhibit improvement in carbohydrate intolerance, as evidenced by a reduced requirement for insulin. Complete reversal of insulin requirement does not occur, however, nor would it be expected in view of the selective destruction of islet B cells.

Pituitary. The anterior pituitary gland is a major site of iron deposition.[31] The gonadotropic cells are especially targeted and their function impaired. It is not surprising, therefore, that reduction of gonadal function is the most common endocrine abnormality in hemochromatosis except for diabetes mellitus. The clinical presentation is that of impotence and loss of libido in the male, sometimes with accompanying testicular atrophy. In some studies approximately two thirds of male patients with hemochromatosis exhibited low plasma levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), with reduced to absent response to stimulation by clomiphene or by luteinizing hormone-releasing factor (LHRH).[30] This is a pattern diagnostic of gonadal failure secondary to pituitary insufficiency. When the diagnosis for homozygosity for hemochromatosis was made earlier by HLA linkage studies, only 5 of 41 men were found to have hypogonadism.[32]

Although the majority of patients have hypogonadotropic hypogonadism, a few have been described with evidence of primary testicular (Leydig cell) failure as manifested by low levels of plasma testosterone and elevated levels of gonadotropic hormones (LH and FSH) together with failure to respond to exogenous gonadotropic stimulation.[33] Other hormones of the anterior pituitary gland are usually secreted normally, or else abnormalities in their secretion are demonstrable only by sophisticated endocrinologic studies.

Patients with hemochromatotic cirrhosis and hypogonadism differ from those who have alcoholic cirrhosis and hypogonadism not only in the relative specificity of the pituitary lesion but also in their lack of the associated signs of hyperestrinism, such as gynecomastia and spider angiomata.[30] The gonadal deficiency of hemochromatosis is usually irreversible and may require androgen replacement therapy in the male. A few patients have had a return of normal endocrine function following phlebotomy.[32]

Hypogonadism is rarely seen in women with hemochromatosis, presumably because of their lower iron overloads and the usual presentation of the disease in women after the time of menopause. In one study of 23 women with hemochromatosis, none had any laboratory evidence of gonadotropin deficiency and none had had a premature menopause or loss of libido.[32] A few younger women with hemochromatosis have been reported to have amenorrhea, with response to the removal of iron.

In summary, the gonadotrope of the adenohypophysis shares with the B cell of the pancreatic islet a special susceptibility to iron injury. As a result, impotence and loss of libido in men may be subtle early manifestations of hemochromatosis. Although other isolated endocrine abnormalities have been sporadically reported in hemochromatosis, their association with this common metabolic disorder may be fortuitous. In contrast to some of the other manifestations of hemochromatosis, endocrine deficiency is usually irreversible.

Skin. Increased pigmentation of the skin was noted early as a manifestation of hemochromatosis as "bronze diabetes." In one series of 100 cases, hyperpigmentation was noted in 98%,[34] but with more sensitive recent methods for earlier diagnosis this sign of hemochromatosis is much less frequently found. The increased pigmentation, classically described as slate-gray or metallic gray but often shading into brown, is usually diffuse but tends to be exacerbated in exposed areas, in the external genitalia, in the nipple areola, and in flexion folds. Approximately 20% of patients have associated hyperpigmentation of the buccal mucosa and conjunctivae. Pathologically, both melanin and dermal iron are increased, the latter occurring most typically as siderosis around eccrine sweat glands. The shade of pigmentation and the relative degrees of melanosis and siderosis correlate poorly. With phlebotomy the skin pigmentation tends to lighten with the loss of siderosis, but some excess of melanin remains. The pathogenesis of melanosis in iron overload states is unclear.

Other dermal manifestations of hemochromatosis include (1) atrophy, often with scleroderma-like changes, most prominently in a pretibial location; (2) ichthyosis, varying from simple xerosis to generalized ichthyosis vulgaris; (3) koilonychia, together with longitudinal striations and brittleness of the nails; and (4) loss of body hair, including pubertal hair.[34] The latter may be related to gonadal failure.

Heart. The heart is frequently involved both pathologi-

cally and clinically in patients with hemochromatosis. Approximately one third of patients with untreated hemochromatosis die of cardiac failure. For reasons that are obscure, this is particularly common with severe hemochromatosis that presents clinically in early life. In the heart, iron deposits in the sarcoplasm of the myocytes with little or none being deposited in the interstitium.[35] The ventricles are more involved than the atria. Degeneration and necrosis of muscle fibers may result, but there is comparatively little inflammation or fibrosis. These findings are readily demonstrable by endomyocardial biopsy.[36] The most frequent resulting abnormality is that of dilated cardiomyopathy (dilated ventricles, reduced ejection fraction) with congestive heart failure. Much less commonly there is restrictive cardiomyopathy that may resemble the clinical picture of constrictive pericarditis. The ventricular wall is usually normal in thickness.[37] Atrial tachyarrhythmias are often observed. The electrocardiographic findings are nonspecific, most commonly showing ST and T wave changes with or without low voltage.

The cardiomyopathy of hemochromatosis is potentially reversible with the removal of iron, but this may be a prolonged process. With severe cardiac involvement, many patients die during the months necessary for effective removal of the iron overload.

Bone and Joints. In a recent study osteopenia was found in 10 of 22 men with hemochromatosis,[38] confirming and extending previous observations. By means of spinal radiography, spinal and forearm bone mineral density estimations, dynamic skeletal histomorphometry, and biochemical measurements the osteopenia was determined to be that of osteoporosis. No evidence of osteomalacia or osteitis fibrosa (hyperparathyroidism) was found. The osteoporosis was found to be associated with evidence of both inadequate bone formation and excessive bone resorption. The radiographic changes seen in bone adjacent to joints involved in hemochromatotic arthritis are described below.

Arthritis is now the most common clinical manifestation of hemochromatosis[39] and not infrequently is the first evidence for the presence of the disease. Approximately 50% of patients develop arthritis, although the percentage tends to be higher in women than in men. How iron overload leads to arthritis has not been established. In hemochromatosis iron can frequently be demonstrated in chondrocytes and in synovial lining cells, particularly in those that are synthetic rather than phagocytic,[40] but there is poor correlation between the histologic findings and the clinical or radiographic abnormalities. When effusions are present, they tend to be noninflammatory except when there is microcrystalline synovitis of pseudogout associated with calcium pyrophosphate dihydrate (CPPD) or hydroxyapatite crystals. Ferric ions inhibit the action of pyrophosphatase and in that manner may increase the local concentration of pyrophosphate and its tendency to crystallize. The potential role of iron to produce oxidant injury has been described already. The relative frequency with which joints are involved in hemochromatosis is shown in Table 3.

Many of the features of arthritis in hemochromatosis resemble those of degenerative joint disease, and this misdiagnosis is frequently made. Notable is the frequency of associated chondrocalcinosis, occasionally complicated by pseudogout. More typical is a form of chronic arthritis in-

TABLE 3.—*Joints Involved in the Arthropathy of Hemochromatosis (Percentage of 159 Patients)**

Metacarpophalangeal	48%	Hips	30%
Proximal interphalangeal	47%	Wrists	28%
Knees	45%	Shoulders	27%
Back and neck	36%	Distal interphalangeal	21%
Feet	32%	Ankles	10%

*From Schumacher HR, Straka PC, Krikker MA, et al: The arthropathy of hematochromatosis: Recent studies. Ann NY Acad Sci 1988; 526:224.

Figure 9.—An oblique radiograph of the metacarpophalangeal joints demonstrates typical changes consisting of narrowing of joint spaces, subchondral sclerosis, collapse of subarticular bone producing a "squared-off" configuration, and prominent "teardrop" osteophytes. (Courtesy of Harry K. Genant, MD.)

Figure 10.—PA radiograph of the hand demonstrates generalized osteopenia of the osseous structures, chondrocalcinosis of the triangular cartilage at the wrist, and degenerative changes at the metacarpophalangeal joints, all characteristic of the osteoarticular changes of hemochromatosis. (Courtesy of Harry K. Genant, MD.)

volving the metacarpophalangeal and proximal interphalangeal joints of the second and third digits.[40] This characteristic presentation is often mistaken for seronegative rheumatoid arthritis or for degenerative joint diseases. Certain radiographic findings in the hands strongly suggest the presence of hemochromatosis (Figures 9 and 10):

1. The joint spaces of the affected joints are narrowed with loss of cartilage and delicate cyst formation and with osteopenia in the metacarpal heads.
2. The metacarpal heads tend to be squared off with a type of bone overgrowth that leads to "teardrops" or hooked osteophytes.
3. Chondrocalcinosis may be present in as many as 50% of patients.

These particular radiographic findings, associated with chronic arthritis most prominent in the metacarpophalangeal joints, strongly suggest the diagnosis of hemochromatosis, even in the presence of normal levels of circulating iron.

In general the arthritis of hemochromatosis does not usually improve significantly following the removal of iron by phlebotomy. In one large series (129 patients), only 20% reported that they were better in joint symptoms during or after treatment.[40]

Abdominal Pain. Patients with hemochromatosis not infrequently complain of persistent epigastric or right upper quadrant aching pain.[2,27] Most frequently this pain is associated with cirrhosis, occasionally marking the appearance of a complicating hepatoma; however, often no cause for the pain can be assigned. It tends to improve greatly or to disappear with successful removal of iron by phlebotomy.[41]

Infections. Patients usually manifest hemochromatosis in later life and not infrequently have debility associated with diabetes mellitus, cirrhosis, and/or heart disease. It is not surprising, therefore, that they may develop infectious complications as well. The availability of iron is a limiting factor in the growth of some microorganisms, and the withholding of iron from these microorganisms by the body's binding proteins is considered to be a form of host defense.[42] It follows that patients with hemochromatosis (in whom iron is much more readily available) may be at increased risk for infections caused by such organisms as *Yersinia enterocolitica*,[43] *Pasteurella pseudotuberculosis*, and *Vibrio vulnificus*.[44] Beyond being a limiting nutrient for the invading microorganism, iron overload may possibly impair phagocytosis and may also have a variable number of adverse effects on lymphocytes and macrophages.[45] Despite these effects, an increased susceptibility to infection is not usually a prominent feature of hemochromatosis.

Neoplasms. The marked association of hepatoma with hemochromatotic cirrhosis has been described earlier. An increased incidence of other malignant tumors in patients with excess body iron has been reported[46] and its existence denied.[41] Iron may be carcinogenic when injected into experimental animals, but usually with the production of sarcomas. Iron overloading suppresses the tumoricidal activity of macrophages.[47] It remains to be shown, however, that malignant tumors other than hepatoma occur more frequently in patients with hemochromatosis than in age-matched controls. The nonhepatoma neoplasms that have been noted have not demonstrated any characteristic pattern.

Central Nervous System. In one notable study changes in mental status were found in approximately one third of patients with hemochromatosis.[2] Most frequently observed were lethargy, psychomotor retardation, and inability to think clearly, although progression to disorientation and decreased responsiveness to external stimuli sometimes occurred. These symptoms tended to improve with the removal of iron by phlebotomy. Episodic confusion and dementia have been described in other patients with hemochromatosis.[48] No correlation with central nervous system pathology has been described. The specificity of these manifestations in an older population with chronic debility, cirrhosis, diabetes mellitus, and/or heart disease is difficult to ascertain, but these observations are provocative and warrant careful appraisal of central nervous system function in all patients with hemochromatosis. Peripheral neuropathy has been noted in patients with diabetes or with concomitant alcoholism.

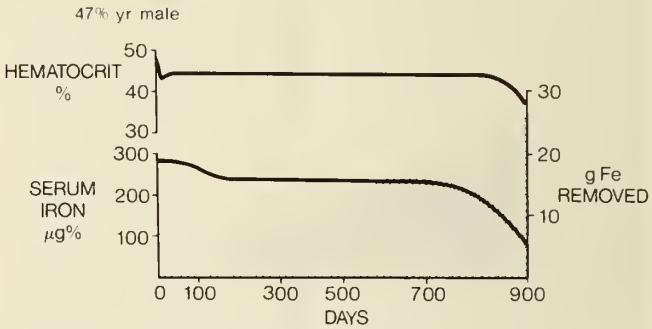

Figure 11.—Response to weekly phlebotomy therapy in hemochromatosis. Patient was a 47-year-old man.

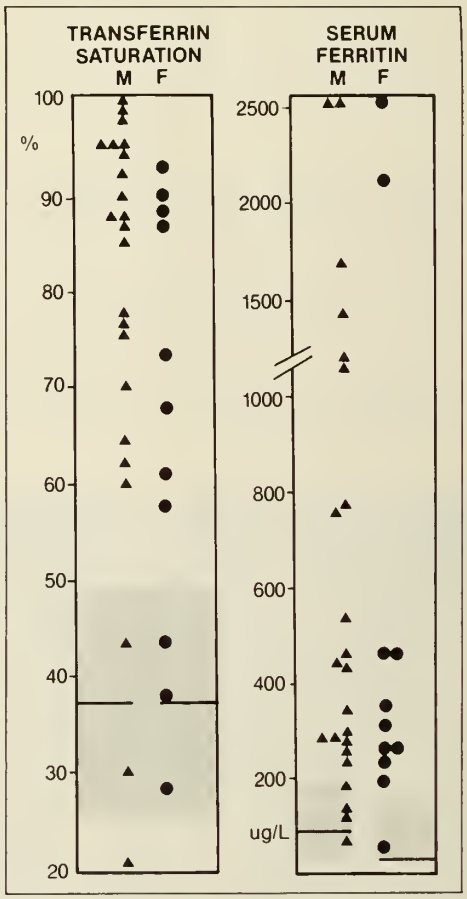

Figure 12.—Transferrin saturation and serum ferritin values in 34 young hemochromatosis subjects. Males=triangles; females=circles. Shaded areas are reference ranges and solid horizontal lines are the normal means. (Redrawn from Bassett ML, Halliday JW, Ferris RA, et al: Diagnosis of hemochromatosis in young subjects: Predictive accuracy of biochemical screening tests. Gastroenterology 1984; 87:628.)

Diagnosis of Hemochromatosis

The diagnosis of hemochromatosis is frequently missed. Certainly the diagnosis is not being established in one out of every 300 to 400 white patients who enter our hospitals and clinics, although virtually all surveys agree that this is the true prevalence of the disease. The first barrier to early diagnosis is that of considering the disease in patients who do not have the triad of cirrhosis, hyperpigmentation, and diabetes but who exhibit other more subtle manifestations of the disease.

In the absence of knowing the gene product that is abnormal or missing in hemochromatosis, the diagnosis depends upon documentation of the secondary phenotypic expression of that abnormality, namely the excessive accumulation of iron. The differential diagnosis is that of other causes of iron overload, as noted already. Within a given family, when an index case of hemochromatosis has been diagnosed by the aforementioned method, other family members can be identified as homozygous or heterozygous by HLA typing, as already described (see Figure 5).

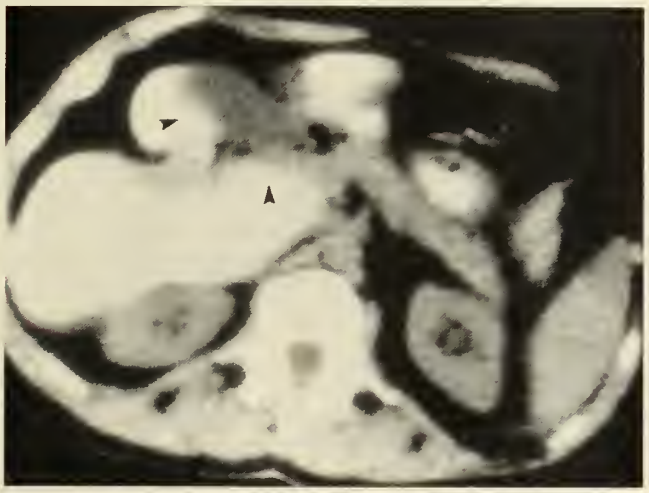

Figure 13.—Computed tomography (CT) showing increased density of the liver in hemochromatosis. The less dense area, indicated by arrows, represents a complicating hepatoma. (Courtesy of Henry I. Goldberg, MD.)

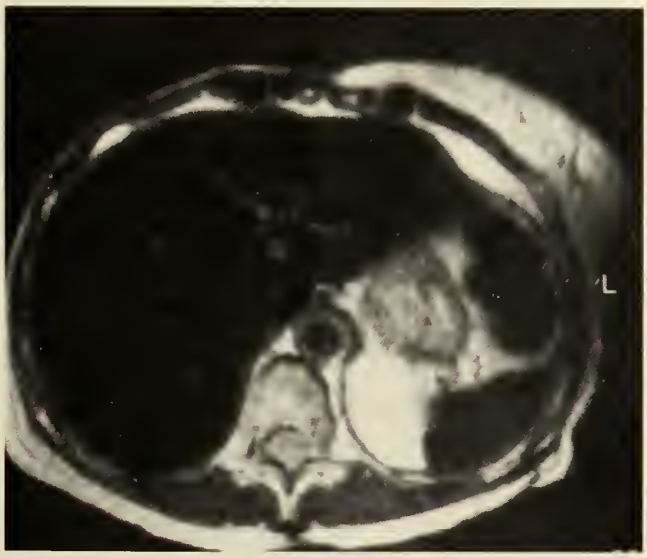

Figure 14.—In this patient with transfusional hemochromatosis the MR image intensity of the liver is markedly reduced compared with that normally seen with this spin echo technique (TR=1.0 sec, TE=28 msec). (From Stark DD, Moseley ME, Bacon BR, et al: Magnetic resonance imaging and spectroscope of hepatic iron overload. Radiology 1985; 154:137.)

The ultimate standard for determining iron overload at this time is that of quantifying its content in hepatic tissue obtained by biopsy, together with a more qualitative analysis of the amount of stainable iron and its distribution. A biopsy also allows an assessment of hepatic damage and fibrosis. The total iron stores can also be approximated retroactively by weekly phlebotomies that are continued until the time of impaired erythropoiesis as a reflection of depletion of these stores. Depending upon the state of circulating erythrocytes, the removal of each unit of 500 ml of blood removes about 200 mg to 250 mg of iron, requiring that the body shift a corresponding amount from tissue stores to heme. Normal stores (~ 1 gram) are depleted by four to five phlebotomies or less; in iron overload, depletion of iron stores from removal of about 1 gram per month (four to five phlebotomies) may require several years (Figure 11).[7] Usually, however, two indirect indices of iron stores are used to survey for the possible presence of hemochromatosis (Figure 12):

1. *Saturation of transferrin.* Plasma transferrin is normally about one third saturated (100 to 120 μg iron per deciliter; 300 to 330 μg iron-binding capacity). In hemochromatosis the saturation of transferrin tends to rise with increasing iron stores. For survey purposes cut-off points of >55% saturation[19] and >62% saturation[49] have been used to define populations at high risk for hemochromatosis. Because of diurnal and also seemingly sporadic variations in plasma iron, borderline findings should be repeated on morning fasting specimens. A transferrin saturation of >70% to 75% is virtually diagnostic of iron overload in an otherwise normal individual. A few younger patients with hemochromatosis, expecially women, will have values <55% saturation.
2. *Serum ferritin concentration.* The level of serum ferritin tends to correlate closely with mobilizable body iron.[9,49] In hemochromatosis, levels are therefore usually above normal (>200 μg per liter in men or >150 μg per liter in women). Serum ferritin levels are sometimes elevated in conditions other than in excessive iron storage, e.g., in the presence of other forms of liver disease, inflammatory reactions, certain tumors, and rheumatoid arthritis. A few patients with hemochromatosis and iron overload have had normal levels of serum ferritin. Nevertheless, taken with transferrin saturation, the measurement of serum ferritin has been a useful survey test.

Other screening tests have been used, such as the total serum iron or the urinary excretion of iron following the injection of a standard amount (10 mg per kilogram) of the chelator protein desferrioxamine, but these tests seem to have less utility.

Newer approaches to noninvasive measuring of body iron are being developed but by and large have not yet reached the stage of validation and availability.[50] These include computed tomography (CT), magnetic resonance imaging (MRI), and magnetic susceptibility measurement (MSM). In CT (Figure 13), most success has come from using a dual energy technique to measure the difference in CT number. In MRI (Figure 14), there is a particularly marked attenuation of the T_2 signal with a resulting "black hole" in the image.[31,51]

Magnetic susceptibility measurement requires a superconducting quantum interference device susceptometer to measure changes in the magnetic susceptibility of the liver secondary to the paramagnetic properties of ferritin and hemosiderin.[50] MSM is a promising new technique that is not yet widely available.

It seems highly probable that future developments in these or analogous physical techniques will allow accurate and convenient assessment of the body's iron stores without the requirement for liver biopsy or the depletion of iron stores by phlebotomy.

When the diagnosis of hemochromatosis is established in a patient, HLA typing should be carried out to allow for diagnosing other cases within the family and for early therapeutic intervention before the onset of organ damage.

Differential Diagnosis of Hemochromatosis (Table 4)

The differential diagnosis is usually not a difficult one, once the possibility of hemochromatosis is considered and the presence of iron overload is established. Iron overload from transfusions is apparent from the history, and the iron burden can be estimated from the number of transfusions received. Iron overload from excessive ingestion in the absence of genetic hemochromatosis is extremely rare except in South African blacks, in whom it has been attributed to iron solubilization from pots used in fermentation in the preparation of beer. Ineffective erythropoiesis, as noted previously, may stimulate excessive absorption of iron. This is seen most frequently in the thalassemias and in some cases of sideroblastic anemia, much more rarely in hemolytic anemia. These hematologic disorders, usually resulting in anemia, should not be difficult to detect, if thought is given to them in the presence of demonstrated iron overload. Sporadic porphyria cutanea tarda (PCT), caused by reduced levels of hepatic uroporphyrinogen decarboxylase, is usually associated with modest (2 to 4 gram) iron overload and usually responds clinically to the removal of this iron by phlebotomy. There is now gathering evidence, however, that these persons are heterozygous (occasionally homozygous) for hemochromatosis.[52] It is presumed that excess hepatic iron is somehow necessary for the phenotypic expression of PCT and that concurrent heterozygosity for hemochromatosis is the most common pathogenesis for creating that excess. The extremely rare genetic condition of atransferrinemia is associated with excessive absorption of iron and siderosis in humans and in a murine model.[13] The most troublesome differential diagnosis is that between hemochromatosis and alcoholic cirrhosis with hepatic siderosis, in which both transferrin saturation and plasma ferritin levels may be increased as well. In alcoholic cirrhosis, however, the Kupffer cells tend also to contain stainable iron, in contrast to hemochromatosis, but more importantly the levels of hepatic iron never reach those seen in hemochromatosis. The total excess hepatic iron in alcoholic cirrhosis rarely exceeds 1 to 3 grams. The presence of genetic hemochromatosis can be further strengthened if a sibling heterozygote or homozygote, determined by HLA typing, shows evidence of iron overload.

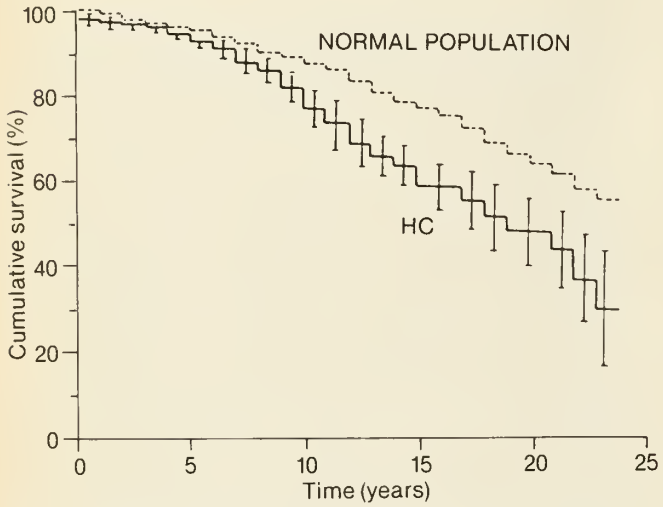

Figure 15.—Cumulative survival in 163 patients with hemochromatosis. The vertical bars represent the calculated 95% confidence interval. (Reprinted with permission from Niederau C, Fischer R, Sonnenberg A, et al: Survival and causes of death in cirrhotic and in noncirrhotic patients with primary hemochromatosis. N Engl J Med 1985; 313:1256.)

Treatment of Hemochromatosis

As an autosomal recessive genetic disease, hemochromatosis cannot currently be cured by replacing the presumably absent or defective gene product. Since all of the known adverse effects of hemochromatosis seem to be caused by the pathologic burden of iron, the primary treatment of the disease is to remove the excess iron as rapidly as is feasible. This is accomplished most effectively by re-

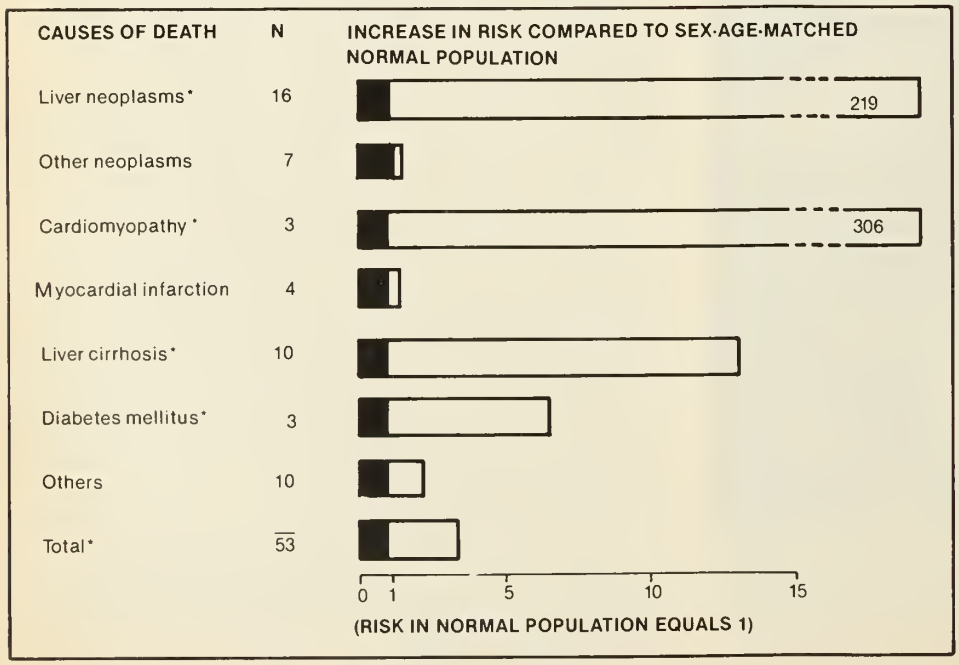

Figure 16.—Causes of death in 53 patients with hemochromatosis. Also shown is the relative risk of dying from each specific cause as compared with a matched control population. The values marked by asterisks are considered statistically significant (fall outside the 95% confidence limit). (From Strohmeyer G, Niederau C, Stremmel W: Survival and causes of death in hemochromatosis. Ann NY Acad Sci 1988; 526:245.)

TABLE 4.—*Differential Diagnosis of Iron Overload*

Hemochromatosis
Repeated transfusions
Hereditary anemias (ineffective erythropoiesis)
Alcoholic cirrhosis
Excessive ingestion of iron (rare)
Porphyria cutanea tarda
Atransferrinemia

peated phlebotomy. In the process of replacing the erythrocytes, the bone marrow then mobilizes iron from storage ferritin and hemosiderin. With a weekly phlebotomy, about 10 to 13 grams of iron can be removed annually. To deplete the iron stores in hemochromatosis may therefore require two or even three years of therapy. The hematocrit and the level of plasma ferritin are usually followed as guides to therapy (see Figure 11). After the removal of the excess iron, maintenance therapy by phlebotomy is required, usually four to six times annually, to counteract the continued excessive absorption of iron that characterizes the disease. This simple program suffices for the treatment of most patients. Rarely, in the presence of severe hemochromatotic heart disease it is important to supplement the phlebotomy program with the continuous infusion of desferrioxamine to accelerate the removal of iron and to protect the patient from further deterioration of cardiac function during therapy. In the face of iron overload, ascorbic acid should be given with great caution since there is evidence that it may mobilize intracellular iron and participate in the peroxidation of lipids to exacerbate iron injury.[21,53]

The treatment of the complications of hemochromatosis will not be discussed here. They include in individual patients the treatment of diabetes mellitus, liver failure, chronic arthritis, deficiency of sex hormones, and congestive heart failure. The importance of surveying family members for the presence of hemochromatosis has been previously emphasized.

Prognosis

Many patients with hemochromatosis have few symptoms that can be clearly attributed to the disease and relatively little disability, and they survive normally to die of other causes. This is the lesson that has been learned from the extensive population surveys that have been carried out, supplemented by HLA haplotype identification of other members within families. This presumably is the major explanation for the marked disparity that exists between the now-accepted prevalence of homozygous hemochromatosis of 3 to 4 cases per 1,000 people of European origin and the comparative rarity with which the disease is diagnosed, even at autopsy.

The cumulative survival of a large series of patients with hemochromatosis compared with that in an age- and sex-matched control group is shown in Figure 15.[41] It is important to note that these patients were all treated by phlebotomy, although some did not survive to allow completion of the removal of iron, and that they tended to represent relatively advanced symptomatic cases. (Only 10% had no cirrhosis or hepatic fibrosis.) In patients without cirrhosis overall survival time did not differ from that in the control population. Not unexpectedly, survival in hemochromatotic patients with diabetes was less favorable than in those without this complication.

The causes of death in 53 patients with symptomatic hemochromatosis are shown in Figure 16, together with a calculation of the relative risk of death from that cause in hemochromatosis as compared with an age- and sex-matched control group.[41] Liver neoplasms (13 hepatomas and 3 bile duct carcinomas) were the most frequent cause of death, with an increased risk of 200-fold. As noted previously, hepatoma occurs only in the presence of cirrhosis, but the risk continues even after successful removal of iron.

Summary

Hemochromatosis is an autosomal recessive genetic disorder that occurs with high prevalence in populations of European origin. The gene that is abnormal in hemochromatosis is found on the short arm of chromosome 6 in close proximity (~1 centimorgan) to HLA-A, but the product coded for by that gene is unknown. The pathogenetic mechanism in hemochromatosis is that of continued, excessive absorption of dietary iron with loss of normal control mechanisms, leading to a gradual but vast expansion of storage iron as ferritin and especially as hemosiderin. Through mechanisms that probably include peroxidation of lipid membranes, the excess iron injures hepatocytes, islet B cells, gonadotropes in the anterior pituitary, myocardium, synovial cells, and chondrocytes, and probably other cells and tissues as well. Most patients with hemochromatosis remain undiagnosed throughout life. Removal of the excess iron by phlebotomy will prevent all of the complications of hemochromatosis when begun early and will significantly improve survival in virtually all patients. It is important, therefore, that the diagnosis of hemochromatosis be considered much more frequently in clinical medicine in order that this effective therapy be utilized.

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Important Advances in Clinical Medicine

Anesthesiology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in anesthesiology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers, or scholars to stay abreast of these items of progress in anesthesiology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Anesthesiology of the California Medical Association, and the summaries were prepared under its direction.

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Glucose Administration During Neurosurgical Procedures

THE ROUTINE USE OF glucose-containing solutions during surgical procedures has recently been questioned, and the potential risks and benefits of glucose administration have been reexamined. Intraoperative hypoglycemia is unlikely to occur in the majority of adult patients who receive glucose-free intravenous solutions during a major operation. Conversely, even moderate rates of glucose infusion may magnify the tendency for blood glucose levels to increase intraoperatively during major surgical procedures. Considerable evidence that hyperglycemia augments neurologic damage caused by global cerebral ischemia has led to the recommendation that intraoperative glucose administration be avoided in patients at risk for cerebral ischemia.

Rhesus monkeys receiving a glucose load before cardiac arrest were noted to have increased neurologic damage compared with food-deprived monkeys. Subsequent studies in a variety of animal species, including primates, have confirmed the deleterious effect of hyperglycemia on the neurologic outcome in models of global ischemia. This effect occurs in animals with relatively modest elevations of blood glucose concentration.

Clinical studies have shown an association between elevated blood glucose concentration and poor neurologic outcome following cardiac arrest in humans. In these patients, however, the hyperglycemia seen with more severe injury may be the result of the neurohumoral response to stress rather than the cause of the injury. Although a correlation between hyperglycemia and an exacerbation of brain damage due to global ischemia has not been confirmed in humans, documentation in a variety of animal models suggests the effect is unlikely to be species-specific.

The mechanism whereby glucose administration exacerbates ischemic neuronal injury is not known. An accepted hypothesis is that the effect is related to increased lactic acid accumulation due to anaerobic glucose metabolism when the brain glucose level is elevated during an ischemic insult.

The influence of glucose administration on focal cerebral ischemia is considerably more controversial. Factors that may alter the effect of blood glucose concentration on focal ischemic injury include the site of injury, the existence of collateral circulation, and whether the ischemic injury is transient or permanent. A correlation between increased glucose concentration and poor neurologic outcome has been shown in a number of clinical studies of patients with acute cerebral infarction, but other studies have failed to corroborate this association. Hyperglycemia has been shown to exacerbate neurologic damage in some animal models of focal cerebral ischemia. In other animal models, hyperglycemia appears actually to exert a protective effect.

In summary, although the adverse effect of hyperglycemia on neurologic damage associated with global cerebral ischemia has been fairly conclusively demonstrated, the influence of hyperglycemia on focal ischemia is not well defined. Patients undergoing neurosurgical procedures are frequently at risk for focal ischemia. Further investigation is needed to clarify this potentially important issue in the care of neurosurgical patients.

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Developing Standards for Patient Monitoring During Anesthesia

AN ANALYSIS OF ANESTHETIC CASES resulting in serious morbidity or death has revealed that many could be prevented with better monitoring. During the 1980s at Harvard Medical School, the anesthesia department in conjunction with their risk management team developed specific monitoring standards to be followed in that institution. These standards, published in 1986 in *The Journal of the American Medical Association,* became the first nationally published standards governing minute-by-minute anesthesia care. The American Society of Anesthesiologists (ASA) adopted a similar intraoperative monitoring standard in 1986.

These initial standards established a maximum time interval of 5 minutes between measuring the blood pressure and the heart rate. Continuous monitoring of the heart by electrocardiogram and of the amount of inspired oxygen by an oxygen analyzer are required. If a ventilator is used, a disconnect alarm must be functional. Auscultation of the heart and breath sounds or other continuous mechanical monitoring of these variables was part of the standards. Also required are the ready availability of equipment to measure the patient's temperature and the continuous presence with the patient of the anesthesia personnel. Exceptions to some of these guidelines are infrequently allowed.

In 1989 the ASA amended these standards to require quantitative methods of assessing blood oxygenation—that

is, pulse oximetry. Strong encouragement to include continuous end-tidal carbon dioxide measurement as a standard should lead to its adoption soon. Certainly other monitoring capabilities will be included as technology makes them available.

During the past three years similar standards for all anesthetics have been adopted in New Jersey, New York, and Massachusetts, and many other states are currently contemplating their own standards. The ASA has attempted to work closely with the legislatures to make this legislation acceptable on a practical and medicolegal basis.

Have these standards improved patient safety? Malpractice carriers seem to think they are beneficial because several gave immediate discounts to anesthesiologists adopting these standards. In addition, anesthesiology may be the only medical specialty to see its malpractice rates drop during the past several years as insurance companies downgraded its risk category. During this time, critics point out, newer anesthesia equipment has been introduced, better-trained anesthesia personnel have entered practice, and safer drugs have been developed. What effect each of these factors has had on patient safety is not certain, but preliminary data through 1988 since Harvard adopted its monitoring standards have shown a trend toward a 70% reduction in preventable anesthetic accidents. Anesthesia monitoring standards are clearly here to stay, and specific practice standards will continue to be added in the future.

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Noninvasive Cardiac Output Measurement

THERMODILUTION CARDIAC OUTPUT is often measured to evaluate heart function in critically ill patients or patients undergoing a major operation. Pulmonary artery catheterization, which is required to measure the thermodilution cardiac output, has potentially serious complications, such as malignant arrhythmia, pneumothorax, and even death. It has recently been proposed that these risks do not outweigh the benefits of pulmonary catheterization. Thus, noninvasive cardiac output measurement techniques become attractive if they can provide some benefits of pulmonary artery catheterization—that is, cardiac output measurement—with reduced patient risk.

Two types of noninvasive cardiac output measurement are currently available: thoracic bioimpedance and Doppler ultrasonography. In thoracic bioimpedance, electrodes are placed on the patient's neck and thorax, and a high-frequency microcurrent is injected into one set of electrodes, with differences in the current detected by another electrode set. Pulsatile changes in the thoracic electrical resistance (impedance) are attributed to cardiac systole and used to calculate the stroke volume. Doppler ultrasonography measures cardiac output by measuring aortic blood velocity. The integral of the aortic blood velocity during systole, when multiplied by the cross-sectional area of the aorta, yields the stroke volume. Ascending aortic blood velocity can be measured at the suprasternal notch and inside the trachea (at the tip of an endotracheal tube). Descending aortic blood velocity can be measured from the esophagus (at the tip of an esophageal probe).

Each noninvasive method has different advantages and disadvantages. Bioimpedance electrodes are easily applied and can provide continuous estimates of cardiac output but are sensitive to electrical interference. Doppler techniques generally measure the aortic blood velocity well, but their absolute accuracy depends on knowing the aortic cross-sectional area. Using a cross-sectional aortic area derived from a nomogram decreases the accuracy, and measuring the aortic diameter with other techniques such as two-dimensional or M-mode echocardiography requires highly skilled examiners. Further, the cross-sectional area of the aorta may not be constant.

Thoracic bioimpedance, esophageal Doppler, and transtracheal Doppler can measure the cardiac output continuously, but suprasternal Doppler can measure cardiac output only intermittently. Both techniques have variable agreement with thermodilution. Some of the difference between thermodilution and the noninvasive methods may be due to a variability in the thermodilution measurement itself rather than the noninvasive measurement.

In their current form, neither bioimpedance nor Doppler ultrasonography can totally replace thermodilution cardiac output measurement. It is hoped they will either prove to be useful in following trend changes in cardiac output or that their technology will be further improved until they can be substituted for thermodilution cardiac output measurements.

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Transdermal-Mucosal Sedative and Analgesic Delivery

ALTHOUGH THE SKIN AND MUCOSAL MEMBRANES of the mouth and nose have long been used for drug delivery, until recently these sites had been overlooked as locations for administering analgesic and sedative-hypnotic drugs. In the past few years, however, research and clinical testing of nonparenteral, noninvasive routes of anesthetic delivery have been active. New vehicles including skin patches, nasal sprays, buccal tablets, and lozenges on a handle have been developed to enable the safe, simple, and efficacious delivery of transdermal and transmucosal anesthetics. Certain patient groups such as children will benefit from these new technologies because an intravenous or intramuscular injection will no longer be necessary for the delivery of potent anesthetics and analgesics. Patient compliance may be greatly improved—compared with that with orally ingested pills—as sustained-release systems using transdermal and transmucosal delivery permit less-often dosing schedules. The clinical application of transdermal and transmucosal anesthetic and analgesic systems includes preoperative sedation and lessening of anxiety, acute postoperative analgesia, and the treatment of chronic pain.

The preoperative administration of sufentanil citrate or midazolam hydrochloride nasal aerosols to children is a simple, relatively pain-free method of reducing the stress

and anxiety of impending anesthesia and surgery. Undiluted sufentanil can be administered in doses ranging from 1 to 2 μg per kg with a rapid (within 10 minutes) onset of sedation and willing parental separation. Midazolam is given in doses ranging from 0.1 to 0.3 mg per kg with similar effects. One disadvantage of this technique is that most children cry briefly from irritation of the nasal mucosa. Children receiving intranasal premedication (especially sufentanil) must be monitored closely because respiratory depression may occur.

Buprenorphine hydrochloride is a long-acting, highly potent, mixed-opioid agonist-antagonist that is well absorbed sublingually owing to its high lipophilicity. Unlike buccal or sublingual morphine sulfate, which has a bitter taste, sublingual buprenorphine is taken well by children. A single dose provides excellent, long-lasting (up to eight hours) postoperative analgesia with less drowsiness and sedation compared with comparable doses of intramuscular morphine or meperidine hydrochloride. Although Buprenex (injectable) has been approved by the Food and Drug Administration (FDA), sublingual buprenorphine (tablet) has not been approved for clinical use in the United States. Several reports of long-lasting respiratory depression not easily reversed by administering naloxone hydrochloride may adversely affect regulatory approval.

Oral transmucosal fentanyl citrate is a fentanyl-impregnated sucrose-based lozenge that has a handle attached to it. As patients suck on the lozenge, fentanyl is released to the oral mucosa for absorption. The patient or clinician is able to regulate delivery by removing the lozenge when the desired clinical effect (sedation or analgesia) is reached. This novel delivery system has obvious appeal, especially to children, because it is easy to administer and pleasing to taste. While not currently approved by the FDA for routine clinical use, transmucosal fentanyl in doses ranging from 10 to 20 μg per kg has been tested in clinical trials for pediatric premedication, postoperative analgesia, sedation for emergency department procedures, and the treatment of breakthrough cancer pain.

Even though the skin is difficult to penetrate, a fentanyl controlled-release skin patch (TTS-fentanyl) has been developed that allows systemic absorption. The patch releases fentanyl at a rate of 100 μg per hour and provides steady-state plasma concentrations for as long as the patch is in place. After the patch is removed, plasma fentanyl concentrations decrease slowly (elimination half-life is 18 to 21 hours), reflecting continued absorption from a reservoir in the stratum corneum. Thus, a rapid termination of drug action would be difficult if the patch had to be removed for opioid-related side effects. Nonetheless, TTS-fentanyl affords excellent, long-lasting postoperative analgesia without the discomfort and erratic absorption that occurs with intramuscular injections. While not currently on the market, TTS-fentanyl is undergoing regulatory approval by the FDA.

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Pain Management in Children

A WEALTH OF INFORMATION about the mechanisms of pain and pain management in children has proliferated in the professional literature. Still, children remain an underprivileged class in terms of access to therapeutic interventions for pain because many physicians do not fully appreciate the existence or perceptions of pain in children or the rational risks of pharmacologic intervention. Perceptions and tolerance of pain are highly subjective and extremely variable in the adult population. In children, the problem of assessing pain becomes much more problematic. Pain perception is usually associated with strong emotions that are assumed by many not to be present in young children, especially neonates. Many sources of bias and misinformation exist that often obviate appropriate pain therapy for children. These include assumptions that infants have no memory, so they will not be affected by the pain experience; children lack a well-developed nervous system, which prevents them from experiencing pain; and the adverse effects of analgesics and anesthetics are already considerable and are only compounded when used in combination with additional postoperative pain therapies. A review of biochemical, physiologic, and histologic evidence has largely dispelled these beliefs.

To respond appropriately to a child's pain, a physician must be able to recognize the existence of the pain. The most obvious clues are changes in behavioral responses such as fluctuation in heart rate, changes in respiration, palmar sweating, and increases in intracranial pressure that may be observed with the performance of invasive procedures in neonates. Additional diagnostic information can be obtained from a working knowledge of a child's various cognitive and maturational levels or from pain assessment tools involving subjective, behavioral, or physiologic measures. With preverbal children, physiologic and behavioral measures are most often employed. Direct reporting measures, such as visual analogue, face, and color scales to represent levels of pain, have also been effective in characterizations of pain in verbal children.

Although the intramuscular use of opiates remains the most commonly accepted method of pain relief in the pediatric population, regional neural blockade is perhaps another effective means of providing postoperative pain relief in children. Appropriate patients, drugs, and types of regional blocks must be selected carefully. The duration of the blockade can be extended with the use of indwelling catheters placed in the epidural, caudal, or intrathecal space or adjacent to various neural plexuses such as the brachial plexus. A catheter can be inserted safely into the caudal space and threaded to the midthoracic level to provide profound pain relief from a thoracotomy incision. When given in conjunction with opioids, local anesthetics can provide a longer duration of pain relief. Epidural bupivacaine hydrochloride, 0.1% to 0.125%, plus fentanyl, 2 μg per ml, infused at 0.2 to 0.4 ml per kg of body weight per hour provides excellent postoperative pain relief. Examples of the use of regional anesthesia include patients with cystic fibrosis who have suffered rib fractures. When treated with continuous epidural local anesthetics, they are more comfortable and demonstrate improvement in their respiratory status. Epidural blockade has also been used to improve regional blood flow to the extremities in patients with purpura fulminans due to meningococcemia and in patients with Kawasaki's disease. A number of regional anesthetic techniques commonly used in children have been recently reviewed.

The use of patient-controlled anesthesia (PCA) devices

in children has gained broader acceptance in the anesthesia community. The efficacy of these devices stems from their ability to maintain a constant minimum blood concentration of analgesic. This is in contrast to the erratic levels that typically occur with the use of intramuscular analgesia. The use of PCA devices obviates the need for intramuscular injections, a source of anxiety and discomfort for children. The PCA devices have been especially useful in patients with sickle cell disorders and have been used for children as young as 5 years. Patients must be carefully screened and instructed before PCA therapy. A morphine sulfate concentration of 1 mg per ml is used at UCLA Medical Center. Bolus doses of 0.015 mg per kg can be self-administered at a predetermined interval, typically 10 minutes. The maximum 4-hour dose that patients can give themselves is usually set at 0.25 mg per kg. The bolus dose, basal infusion rate (constant background infusion rate), and lockout period (mandatory time interval between doses) can be independently varied to each patient.

Although children in pain are also seen in emergency departments, pain management is often overlooked there. A wide variety of agents including nitrous oxide in a 50/50 mixture with oxygen, midazolam given rectally or intranasally (0.3 mg per kg), and ketamine hydrochloride (0.5 mg per kg) given intravenously will safely alleviate pain and anxiety.

Prophylactic and adjunctive nonsteroidal anti-inflammatory therapy has long been advocated for the treatment of cancer and joint pain. An intravenous preparation of indomethacin, a nonsteroidal anti-inflammatory agent, has been efficacious in treating postoperative pain in children.

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Intravenous Propofol Anesthesia

THE DEVELOPMENT OF THE DRUG propofol, which is characterized by a rapid onset and termination of action, and advances in the design and capabilities of infusion pumps, have led to a renewed interest in the use of intravenous techniques for the maintenance of anesthesia. It is now possible to titrate an intravenous infusion of propofol in response to surgical stimuli in the manner in which a vaporizer of a volatile agent is currently used.

After an induction dose is administered to fill the initial volume of distribution, an infusion rate that matches the clearance of the drug will maintain a constant blood level of propofol and anesthesia. As the kinetics of propofol are linear within the range used for continuous infusions, higher or lower concentrations should be easily achieved by changing the infusion rate. These predictions have been borne out in clinical practice, and several infusion regimens have been described.

Comparative studies have found a propofol infusion to be a suitable alternative to induction with thiopental sodium and maintenance with halothane, isoflurane, or enflurane. It is associated with a rapid recovery and a low incidence of nausea and vomiting. When combined with an analgesic and a muscle relaxant, it is suitable for total intravenous anesthesia. By itself, propofol may be used in subanesthetic doses to provide sedation for patients undergoing a surgical procedure under regional anesthesia or for patients in intensive care units. With a reduction of the infusion rate, it may be used safely in the elderly, and prolonged use does not cause adrenocortical suppression.

Side effects that are seen when the agent is used for induction are less apparent than when used for continuous infusion, namely, dose-dependent cardiovascular depression. Metabolism and excretion are not affected by moderate hepatic or renal impairment.

Recent advances in infusion pump technology have greatly simplified and added to the safety of continuous infusion techniques. Small battery-operated pumps can be programmed for an individual drug and patient weight to display the infusion rate in milligrams per kilogram per hour rather than milliliters per hour. This avoids anesthetist error in complex calculations of infusion rates, thereby increasing safety. These pumps have proved to be simple and useful for propofol infusions, where the basal rate can be adjusted to take into account the age of the patient, concurrent drug therapy, and preexisting disease states.

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Alerts, Notices, and Case Reports

Failure to Recognize Late Postpneumonectomy Empyema
Role of Diagnostic Thoracentesis

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POSTPNEUMONECTOMY EMPYEMA, an unusual occurrence, generally occurs soon after pneumonectomy.[1] We describe a case of late empyema necessitatis—extension of an empyema to the chest wall—which presented eight months after the patient had a lung resection for squamous cell carcinoma.

Report of a Case

The patient, a 60-year-old man with chronic obstructive pulmonary disease, underwent a left pneumonectomy for squamous cell carcinoma of the lung in 1986. There were no untoward infectious complications postoperatively.

Five months later, he was admitted to the medicine service with exacerbations of his underlying pulmonary insufficiency. New findings included a temperature of 37.7°C, a pericardial friction rub, splenomegaly, and anemia of chronic disease with leukocytosis. A chest x-ray film showed persistent but unchanged left pleural opacification, compatible with a left pneumonectomy. An extensive investigation failed to elicit a cause for his deterioration. In the absence of localizing symptoms to the left chest, a thoracentesis or chest computed tomographic (CT) scan was not done. The diagnosis was a presumed viral syndrome and the patient was discharged on a regimen of prednisone, 20 mg a day, for his obstructive respiratory disease.

Six weeks later the patient was readmitted for respiratory insufficiency and hemoptysis. His temperature was 38.4°C. There was no pericardial or pleural friction rub, and the splenomegaly had diminished. Laboratory data included a hemoglobin of 100 grams per liter and a leukocyte count of 19 × 10^9 per liter, with a polymorphocytic predominance. A chest roentgenogram was unchanged from previous postoperative films. One week later, a bulging left axillary mass developed abruptly. A contrast-enhanced chest CT scan was done (Figure 1). The patient underwent surgical drainage of a 3-liter empyema necessitatis. No recurrence of carcinoma or bronchopleural fistula was found. Cultures of the purulent fluid grew *Streptococcus viridans* and anaerobic peptococci. The patient is alive two years later.

Comments

Empyema necessitatis was mainly seen in the prechemotherapy era with tuberculosis and, now, after resection for pulmonary carcinoma.[2] As many as 25% of cases of postpneumonectomy empyema occur late, or more than 1 month to 25 years after the operation.[3] A delay in diagnosis of several months is the rule.[2]

After a pneumonectomy, fluid that has accumulated in the pleural space clots and becomes a fibrotic mass, but the cavity is not completely obliterated. Isolated areas of fluid may persist for years and be a nidus for bacterial seeding, either by direct extension from a fistula or by hematogenous spread.[2,4] Risk factors for the development of postoperative empyema include the size of resection; pneumonectomy confers the highest risk.

This case shows the difficulty in the diagnosis of late postpneumonectomy empyema. The postoperative course is unremarkable for most patients.[2] Symptoms of the empyema are mainly infectious and constitutional and may resemble an influenzalike syndrome. Often there are no localizing signs to the chest.[2] In retrospect, the presence of a pericardial friction rub was suggestive of a contiguous infection.

The absence of gas on a chest x-ray film does not rule out a postpneumonectomy empyema. If the cause of the empyema is a fistula, either bronchopulmonary or esophagopulmonary, gas is generally seen on a chest film that had previously shown postoperative opacification. In patients with late-onset postpneumonectomy empyema in whom empyema necessitatis develops, a fistula tends not to be the cause of the infection and, therefore, these patients do not have gas on the chest radiograph.[2] In our patient, extension of the empyema to the chest wall probably occurred because there was no means of decompression through fistulization to either a bronchus or the esophagus.

When a patient with a previous pneumonectomy, no matter how long ago, is undergoing an evaluation for a source of infection, the pneumonectomy space must be considered as a possible site. Computed tomographic evaluation of the pneumonectomy space may be of some help.[5] Fluid-filled spaces, as well as re-expansion of the postoperative hemithorax with mediastinal shift to the midline due to pleural expansion, may be shown. Diagnostic thoracentesis, with ultrasonographic or CT guidance, if necessary, should be strongly encouraged even if lung imaging studies fail to identify the pleural space as a source of infection.[2]

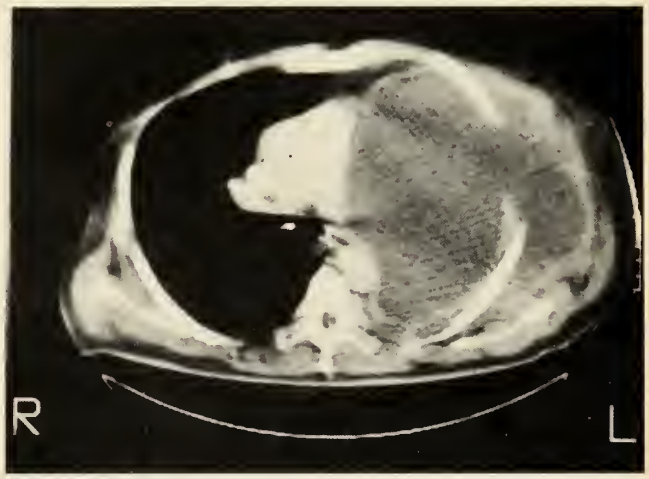

Figure 1.—A computed tomographic scan taken at the level of the main pulmonary artery shows a large left pleural fluid collection that has re-expanded the left hemithorax, shifted the mediastinum back to the midline, and extended into the left chest wall at the site of a previous rib resection.

(Papadakis MA, Wall SD: Failure to recognize late postpneumonectomy empyema—Role of diagnostic thoracentesis. West J Med 1990 Sep; 153:313-314)

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Pericarditis—An Extraintestinal Complication of Inflammatory Bowel Disease

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THE OCCURRENCE of pericarditis in association with inflammatory bowel disease is rare and not widely recognized.[1] Extraintestinal manifestations of inflammatory bowel disease are well recognized, and they may be severe and unrelated to the extent or degree of activity of the colitis.[2] We report a case of pericarditis complicating the clinical course of ulcerative colitis.

Report of a Case

The patient, a 37-year-old man, was admitted to hospital in August 1989 because of weakness, anorexia, nausea, and lower abdominal pain. He had a diagnosis of ulcerative colitis dating 12 years, when he initially had several episodes of rectal bleeding. Over the years, he had isolated exacerbations of his ulcerative colitis, which was confined to the descending colon and rectum and which responded well to a combination of oral prednisone and sulfasalazine. He had taken the sulfasalazine irregularly over the years. His most recent flare-up was six weeks before this admission when he had cramps and diarrhea (four stools per day) with blood and mucus. Following a colonoscopy, he received a short tapering course of oral prednisone for four weeks and sulfasalazine, 2 grams per day, and he had been free of rectal bleeding for the past three weeks.

On admission to the hospital, the patient was afebrile with a pulse rate of 102 beats per minute, and he had a blood pressure of 140/70 mm of mercury. There was evidence of mild postural hypotension in keeping with his dehydrated state. There was no pulsus paradoxus, and his venous pressure was not elevated. Heart sounds were normal, and there was no gallop or pericardial friction rub. The results of the respiratory, abdominal, and neurologic examinations were within normal limits. On the third day in hospital, the patient complained of a substernal chest pain unaffected by posture or respiration. He continued to be afebrile, and his heart rate dropped to 54 beats per minute; there was no pulsus paradoxus, and his blood pressure was 120/80 mm of mercury. Apart from the above, the findings of the physical examination were unchanged from those on his admission. An electrocardiogram (ECG) showed sinus bradycardia with ST segment elevation in all the chest and limb leads except in leads I, aVL, aVR, and V_1 (Figure 1). An echocardiogram did not reveal a pericardial effusion. The creatine kinase level was 430 units per liter; eight hours later, it was 414 units per liter, and the MB fractions were 0.06 and 0.11, respectively. Other laboratory studies included normal serum albumin and globulin levels and a leukocyte count of 16.0 × 10^9 per liter (with a normal differential count). A diagnosis of pericarditis associated with ulcerative colitis was made, and the patient was treated with indomethacin, 25 mg orally three times a day. He rapidly responded symptomatically to this therapy, feeling better in a day. There was no recurrence of his chest pain, and the indomethacin was discontinued after three days without a relapse of his condition. The ECG reverted to normal on the third day.

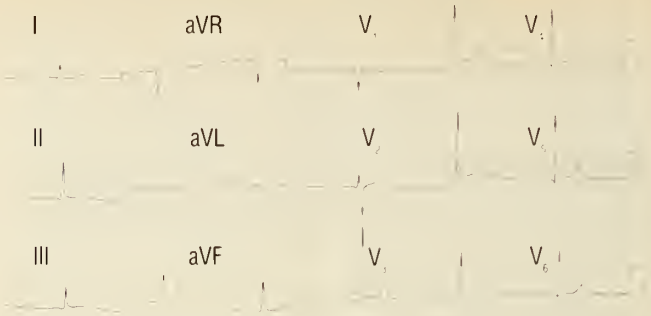

Figure 1.—An electrocardiogram taken on the first day of chest pain shows ST segment changes compatible with pericarditis.

Comment

The wide spectrum of extraintestinal complications of ulcerative colitis and Crohn's disease is well known and includes inflammatory lesions of the skin (pyoderma gangrenosum and erythema nodosum), aphthous buccal ulceration, ocular lesions (uveitis and conjunctivitis), muscular skeletal disorders (arthritis, sacroiliitis, ankylosing spondylitis), vascular complications (thromboembolic disease, vasculitis, arteritis), and a variety of hepatic lesions (fatty liver, pericholangitis, sclerosing cholangitis, cholangiocarcinoma, liver abscess, drug hepatitis, immunopathic chronic active hepatitis, amyloidosis, and cholelithiasis). Pericarditis, myocarditis, and pleural effusions are uncommonly associated with inflammatory bowel disease, yet their association should not come as a surprise in view of their occurrence in other so-called autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis.[1] The pathogenesis of the extraintestinal complications of inflammatory bowel disease is unknown, and the actual frequency of their occurrence is uncertain. In large case studies, between 25% and 36% of patients with inflammatory bowel disease had at least one such associated disease.[3,4] Most cases are associated with ulcerative colitis rather than Crohn's disease. The pericardial complications of inflammatory bowel disease run a course independent of the gut disorder.[5,6] Pericarditis has been reported to antedate the diagnosis of ulcerative colitis by two years, and it can persist despite a remission of the colitis.[6] A report of pericarditis manifesting weeks after a subtotal colectomy for ulcerative colitis indicates the imprecise temporal relationship between the two disorders.[5] The possibility of association between the pericarditis and the medications pre-

(Abid MA, Gitlin N: Pericarditis—An extraintestinal complication of inflammatory bowel disease. West J Med 1990 Sep; 153:314-315)

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scribed for ulcerative colitis has been raised. Sulfasalazine has been effective in resolving the pericarditis, but exacerbations of pericarditis have occurred during the drug therapy. The possibility of a rare association between 5-aminosalicylic acid enemas and pericarditis has been recently raised, and there is little to implicate the 5-aminosalicylic acid enemas as a causative factor relating to the pericarditis.

The pericarditis—and, at times, myocarditis—can range from a mild inflammation to a pericardial tamponade that may require drainage.[7] In the milder presentations, salicylates or nonsteroidal anti-inflammatory agents (indomethacin) are effective therapy. In the more severe cases, the use of prednisone or an intensification of the dosage of steroids (if already prescribed for the inflammatory bowel disease) is recommended. The natural history of the pericarditis varies, and recurrent episodes of pericarditis or myocarditis have been reported.[8] Physicians treating patients with inflammatory bowel disease should always consider pericarditis or myocarditis in the differential diagnosis of chest pain.

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Rattlesnake Capsule-Induced *Salmonella arizonae* Bacteremia

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Salmonella arizonae, described 50 years ago in colonized chuckwallas *(Sauromalus obesus),* horned lizards (genus *Phrynosoma*), and Gila monsters *(Heloderma suspectum)* and known as *Salmonella dar-es-salaam,*[1] was first identified from a human case of pyrexia in the town in east Africa by that name. The organism is part of the normal reptile intestinal flora and, although not pathogenic for snakes and turtles,[2] causes disease in monotremes,[3] turkeys, chickens, goats, and humans.[4] Placed in a separate group by Edwards and co-workers in 1943 and subsequently labeled *Arizona hinshawii,*[5] it is now once again classified under a single species, *Salmonella enterica,* which is subdivided into six subspecies. Based on DNA studies and biochemical tests, *A hinshawii* and *S enterica* subspecies *arizonae* are identical.

S arizonae was recently cultured from blood specimens of two patients at the Eisenhower Medical Center, Rancho Mirage, California. Both patients had Hispanic surnames, suggesting to one of us (Li.A.C.), the District Health Officer of northern Los Angeles County, that the ingestion of rattlesnake capsules, a common practice among Mexican-Americans in the Los Angeles area, could be the cause of infection. We were able to confirm this in one of the two patients and suspect it in the other.

Report of Cases

Patient 1

The patient, a 71-year-old Mexican-American woman, while receiving corticosteroids for rheumatoid arthritis, had fever and chills develop, accompanied by left hip and leg pain. She was admitted to hospital a few days later. Culture of three blood specimens obtained on admission grew out *S arizonae.* A computed tomographic scan of the pelvis revealed findings consistent with an abscess of the left iliac muscle. A subsequent radionuclide bone scan yielded evidence of arthritis involving the left sacroiliac joint. Initial therapy with intravenous ceftriaxone sodium, 2 grams daily for 16 days, in this penicillin-allergic woman failed to eradicate the abscess, which subsequently completely resolved with a regimen of chloramphenicol, 4 grams daily. The patient was then queried as to her use of medications. She readily admitted ingesting several "folk remedies" while in Mexico recently but did not specifically recall the use of rattlesnake capsules. None of these medications were available for culture. *S arizonae* was not identified in a stool specimen.

Patient 2

The patient, a 72-year-old Mexican-American man, had metastatic melanoma develop in late 1988 that involved pleura, lungs, bone, and liver. A regimen of combination chemotherapy using dacarbazine, vinblastine sulfate, cisplatin, and carmustine was started. He was favorably responding to chemotherapy when pancytopenia and fever developed, requiring admission to hospital in January 1989. Culture of three initial blood specimens grew out *S arizonae.* He responded promptly to empiric therapy using vancomycin hydrochloride (later discontinued) and aztreonam. Cultures of blood were subsequently sterile. *S arizonae* could not be identified in stool specimens. The patient readily admitted taking capsules of *víbora de cascabel* (rattlesnake) to assist in the treatment of his metastatic melanoma. More than 50 of these capsules were retrieved and sent to the California State Health Department, and *S arizonae* was identified.

Discussion

The use of rattlesnake powder or meat to treat cancer, diabetes, arthritis, and skin disorders or other sundry ailments is common in Mexican folk remedies. With the rattles left in place for identification, the reptile is decapitated, skinned, dried in the sun, pulverized, placed in capsules, and then sold under various names: *víbora de cascabel, polvo de víbora,* and *carne de víbora.*[6] The capsules are sold without prescription in *farmacias* in Hispanic neighborhoods in Los Angeles and Mexico and are readily available in several communities in California.

(Cone LA, Boughton WH, Cone LA, et al: Rattlesnake capsule-induced *Salmonella arizonae* bacteremia. West J Med 1990 Sep; 153:315-316)

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The rattlesnake capsules ingested by the second patient in this report were purchased in Mexicali, Mexico, just across the United States-Mexico border of California and about 100 miles south of the Eisenhower Medical Center in Riverside County. Although *S arizonae* was isolated from these capsules by the Food and Drug Section of the California Department of Health, different serotypes of *Salmonella* organisms were identified in each lot, indicating the nonuniform distribution of *Salmonella* serotypes in the specimens.

Salmonella infection in humans results in gastroenteritis, enteric fever, bacteremia (septicemia), or localized abscesses. Of the eight previously reported cases of this infection in patients who consumed rattlesnake capsules, seven were bacteremic and three were localized infections.[6-11] These findings stand in contrast to those of reviews of 1959,[12,13] 1967,[4] 1970,[14] 1975,[15] and 1976,[16-18] where two thirds of all *A hinshawii (S arizonae)* infections were localized to the gastrointestinal tract and the remaining third were equally divided between localized infection and bacteremia. The two patients in this study had bacteremia, and in one patient a localized abscess was found in the left iliac muscle. Noteworthy, all 10 patients with rattlesnake capsule-induced *S arizonae* infections were Mexican-American and residents of California (7), Texas (2), and Arizona (1). The two new cases reported in this communication further emphasize the presence of underlying medical disease and immunosuppression, residence adjacent to the Mexican border, and the invasive properties of *S arizonae*. Ampicillin, chloramphenicol, the combination of trimethoprim and sulfamethoxazole, and some β-lactamase-stable cephalosporins[19] are used to treat serious salmonella infections. The lack of response to ceftriaxone is noteworthy in one patient in this study who ultimately responded to the use of chloramphenicol. In addition, one patient was cured with aztreonam therapy, an observation made by us previously.[20]

After this manuscript was submitted, three cases of *S arizonae* bacteremia were recorded in patients with the acquired immunodeficiency syndrome who ingested dried rattlesnake preparations.[21-23]

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Indolent *Staphylococcus aureus* Pneumonia

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Staphylococcus aureus pneumonia is most frequently a rapidly progressive, necrotizing infection with a high mortality rate. This impression is derived in large part from early descriptions of the illness that emphasize an abrupt onset of dyspnea, pleuritic chest pain, prostration, and high fever.[1-3] A chronic, insidious clinical presentation has also been described, however, although rarely reported.[4,5] Because the course is so commonly abrupt with a rapid progression, clinicians have been reluctant to attribute indolent pneumonitis to *S aureus*, even with culture confirmation.

We report a case of indolent *S aureus* pneumonia in a patient with leukopenia and Felty's syndrome. The purpose of this report is to emphasize the subacute presentation of staphylococcal pneumonia and its unusually slow response to therapy. Impaired antibacterial defense of the patient due to Felty's syndrome-induced leukopenia or abnormal neutrophil bactericidal function[6-8] may have been instrumental in the subacute occurrence and the persistence of pneumonia during appropriate antibiotic treatment. Alternatively, avirulence of the organism may have contributed to this presentation.

Report of a Case

The patient, a 43-year-old man, had rheumatoid arthritis diagnosed at age 18. Aspirin therapy was started; intramuscular gold and penicillamine were subsequently used but discontinued two years before admission. Felty's syndrome was diagnosed at that time, and a splenectomy done

(Welsh CH, Watters LC, Harbeck RJ, et al: Indolent *Staphylococcus aureus* pneumonia. West J Med 1990 Sep; 153:316-319)

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a year later without improvement of the neutropenia. Cervicofacial actinomycosis was treated with penicillin eight months before admission and completely resolved. By the time of admission, he had had sweats, right anterior pleuritic chest pain, and a minimally productive cough for 2 weeks and malaise, anorexia, and a 4.5-kg (10-lb) weight loss for a month.

He was cachectic but in no distress; his temperature was 39.4°C (103°F). Rales were present at both bases, without rubs or focal consolidative changes. The liver was 14 cm in span and mildly tender. Chronic deformities of rheumatoid arthritis were present without subcutaneous nodules. Laboratory values were remarkable for a leukocyte count of 1.8 $\times 10^9$ cells per liter (0.1 bands, 0.1 neutrophils, 0.6 lymphocytes, and 0.2 monocytes). The hematocrit was 0.31, and the platelet count was normal. The serum albumin level was 29 grams per liter with a total protein of 79 grams per liter. Arterial blood gas determinations with the patient breathing room air showed a pH of 7.54, Pco_2 3.9 kPa (29 mm of mercury), Po_2 7.3 kPa (55 mm of mercury) and oxygen saturation 0.92. A chest radiograph showed a right upper lobe anterior segment infiltrate and smaller infiltrates in the right lower and middle lobes (Figure 1). A sputum Gram's stain showed scant neutrophils and a few gram-positive cocci; culture grew *S aureus* sensitive to methicillin. Serum protein electropheresis revealed a polyclonal increase in immunoglobulin (Ig) G levels. Quantitative immunoglobulin levels showed an increase in IgA and IgG (12.6 and 23.7 grams per liter, respectively). C3 levels were decreased at 0.58 grams per liter (normal range 0.83 to 1.77).

Transbronchial biopsy was done, and the specimen showed only focal interstitial fibrosis. Ziehl-Neelsen, modified Ziehl-Neelsen, Gram's, and Gomori methenamine-silver stains were negative. Cultures from the biopsy specimen grew small numbers of *S aureus* with the same sensitivity pattern as in the sputum. Cultures were negative for anaerobes, mycobacteria, and fungi. An intravenous regimen of antibiotics, oxacillin sodium, and penicillin was started. Bronchoscopy and biopsy were repeated, adding no new diagnostic information, but culture of specimens again grew *S aureus*. Despite continuous antibiotic therapy over two weeks, daily temperatures rose to 38.9°C to 39.4°C and serial chest radiographs showed progression of the right upper lobe infiltrate (Figure 2). Leukocyte counts remained in the range of 1.0 to 2.0 $\times 10^9$ per liter with 0.2 to 0.5 neutrophils. Transthoracic needle aspiration from the anterior segment of the right upper lobe showed no organisms on Gram's stain or culture. Penicillin therapy was stopped and a course of rifampin added to enhance intracellular bacterial killing by the neutrophils. Because of persistent symptoms, fever, and worsening infiltrates, a thoracotomy was done and biopsies taken of the right middle and lower lobes. These specimens showed necrotizing bronchopneumonia with areas of vascular thrombosis, organizing pneumonitis, and clusters of gram-positive cocci. Interstitial fibrosis, consistent with rheumatoid lung disease, was also present.

Cephradine, 4 grams a day, was substituted for oxacillin despite good sensitivities of the staphylococcus to oxacillin in vitro, and rifampin, 600 mg per day, was continued. Over the next week his temperatures fell, accompanied by subjective and radiographic improvement. A month after admission he was discharged on a regimen of cephradine and rifampin for an additional 10 weeks. Follow-up leukocyte counts have remained at less than 2.0 $\times 10^9$ per liter, and films have shown slow and incomplete resolution of the right upper lobe infiltrate (Figure 3).

Methods

The killing of *S aureus*, a test of granulocyte phagocytic and bactericidal function, was assessed by quantitating the number of viable *S aureus* organisms after incubating with neutrophils.[9] To prepare the neutrophils, 3% dextran in a physiologic saline solution was added to an equal volume of heparinized blood and the mixture allowed to stand for 20 minutes. The leukocyte-rich plasma was recovered, centrifuged at 1,000 rpm for 10 minutes at 4°C, and residual red cells lysed with a hypotonic saline solution and washed. For the bactericidal assay, 2.5 $\times 10^6$ *S aureus* (ATCC 25923 or patient strain) in 0.3 ml Hanks' balanced salt solution (HBSS) containing 0.2% glucose and 0.2% bovine serum albumin, 2.5 $\times 10^6$ granulocytes in 0.6 ml HBSS, and 0.1 ml normal human serum as an opsonin were incubated at 37°C on a rotary mixer. At 30-minute intervals from 0 to 120 minutes, aliquots of the reaction tubes were removed, the leukocytes disrupted in water, diluted, and agar pour plates prepared. The results are plotted as the number of viable bacteria remaining at each sampling time.[9] Data are presented as the mean of two individual assay tube results for each time point, a standard way of displaying these data.[9,10] The experiments were repeated on a second day with similar results.

Results

Granulocyte bactericidal assays revealed decreased neutrophil killing of a virulent *S aureus* strain (laboratory stock, Figure 4-A) plotted as increased *S aureus* viability after incubation with patient but not control neutrophils. Bactericidal studies of granulocytes incubated with the patient's own *S aureus* organisms, however, show that this organism was killed equally well by his granulocytes as by control human granulocytes (Figure 4-B).

Discussion

Unusual aspects of this case include both the insidious nature of a usually fulminant illness and its slow rate of resolution, both of which are atypical features of reported *S aureus* pneumonia, which is characterized by a sudden onset and severe clinical course[1-3] with a 20% to 60% mortality.[3] A benign clinical course has recently been reported in

Figure 1.—A chest radiograph (posteroanterior view) taken at the time of hospital admission shows a right upper lobe infiltrate.

three adults but, in contrast to our patient, these patients had a rapid resolution of symptoms and fever after antibiotic therapy was instituted.[4,5] Patients rendered neutropenic by cancer chemotherapy may have a clinical presentation intermediate in severity. Unlike, however, the reports of *S aureus* pneumonia in neutropenic cancer patients with high (71%) mortality rates,[11] our patient had a protracted course, yet did well. Symptoms of bacterial pneumonia in these patients may be less prominent (cough and sputum production are considerably less common), but fever and infiltrates are equally common to patients with normal leukocyte counts.[12]

Figure 2.—A chest radiograph taken after 10 days of therapy shows progression of the infiltrate.

Figure 3.—A chest radiograph taken after 8 weeks of antibiotic therapy shows incomplete resolution of the infiltrate.

Our patient's low number of circulating neutrophils undoubtedly increased his risk for infection, as neutropenia has been associated with an increased risk of bacterial infection in a variety of disorders, including neutropenia after cancer chemotherapy,[13] chronic neutropenia of childhood,[14] and Felty's syndrome, the triad of leukopenia, splenomegaly, and rheumatoid arthritis.[6,15] Not only is Felty's syndrome associated with a high rate of bacterial infection, but infection remains the major cause of death for patients with severe leukopenia.[15] Altered neutrophil behavior may also increase the risk or attenuate the presentation of infection. An increased susceptibility to infection in Felty's syndrome has been attributed to abnormalities of neutrophil function that include decreased bactericidal activity,[7,16] lessened rates of chemotaxis,[16] a decreased rate and quantity of superoxide production,[8] and defects of phagocytosis.[6,7] Abnormalities of phagocytosis may be due to serum factors such as increased levels of cryoglobulins[7,10] or decreased levels of complement[6] and circulating immune complexes, both of which depress Fc receptor-mediated phagocytosis.[6,16] Our patient had severe neutropenia, low serum C3 levels, abnormal neutrophil bactericidal activity, and a long-term use of high-dose steroids, any of which may have impaired his resistance to infection. Although his neutrophils killed his staphylococcal strain in vitro, they were not equally effective in vivo, as his infection failed to clear despite appropriate antibiotic therapy. Possible reasons for this in vitro-in vivo antibactericidal discrepancy include not only the neutropenia, which was not present in vitro, and abnormalities of circulating serum factors, but also a lack of access of neutrophils to infected lung, as vascular thrombosis was noted on biopsy and neutrophils may have failed to reach all sites of bacterial accumulation. A variety of mechanisms may thus have contributed to his indolent presentation and slow response to therapy.

Differences in bacterial characteristics (virulence) may explain the range of acuity in *S aureus* pneumonia. In particular, a relative decrease in virulence may be associated with a subacute presentation. Our present knowledge of *S aureus* virulence is incomplete, but characteristics known to increase virulence include an increased thickness of the

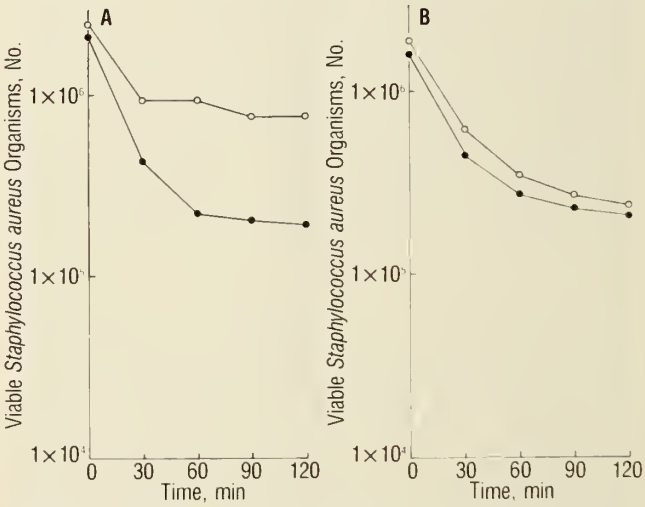

Figure 4—A, Bactericidal activity of granulocytes is assessed, plotted as the number of remaining viable bacteria after incubation with neutrophils from the patient (○) and a normal control (●). *Stophylococcus oureus* strain ATCC 25923, a virulent laboratory strain, is used in this experiment. The patient's neutrophils fail to adequately kill these *S aureus* (62.5% killing versus 90% killing by the normal neutrophils; normal range, 82% to 100%). **B,** Bactericidal activity of granulocytes from the patient (○) and a normal control (●) against the patient's *S oureus* strain is adequate: 87% and 88% killing, respectively.

slime capsule rendering the bacterium resistant to phagocytosis,[17] and the production of toxins such as α-hemolysis[18] or leukocidin,[19] which may inhibit neutrophil chemotaxis. The killing of one but not both strains of *S aureus* as seen on our patient's granulocyte bactericidal assay may imply differences in strain virulence, although at present we lack the diagnostic tools to explore this further.

If the development of clinical bacterial infection involves a balance between the virulence of organisms and adequacy of host defense mechanisms, a spectrum of disease penetrance should be seen. This spectrum may include the elimination of bacteria without clinical illness (avirulent organism or adequate defense mechanisms), indolent infection (avirulent organism or impaired host defense mechanisms), or fulminant infection (virulent organism or adequate defenses). We speculate that our patient had such an indolent course due to a combination of both an avirulent bacterium and abnormalities of neutrophil number and neutrophil bactericidal function.

We report the case of a patient with an indolent course of *S aureus* pneumonia, which has rarely been described in either immunosuppressed or normal hosts. The reasons for the indolent nature of bacterial infection are frequently unknown, but the present case with the accompanying defects of neutrophil number and bactericidal function may account for both the infection's insidious onset and delayed rate of healing. This indolent course should not dissuade physicians from the diagnosis of staphylococcal pneumonia when positive culture evidence exists.

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Ride and Tie

A Hybrid Sport With Synergistic Potential for Injury

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THE COMPETITIVE SPORT of ride and tie has become popular in the past 15 to 20 years, especially in the Rockies and in California. Races generally cover 20 to 40 miles of hilly, often rough terrain. Each team consists of two runners and a horse. During a race, one runner rides ahead on horseback for perhaps a mile, then dismounts, ties the horse to anything available, and continues the race on foot. The partner reaches the horse, unties it, rides up to the first runner, and the two then switch. This process is repeated perhaps 20 to 30 times in a race.

There are now more than 350 races, with an annual international championship. Races may contain 40 to 60 teams with varying levels of skill in both running and riding. The sport offers a multitude of opportunities for injury. The trails are often steep and washed out, a race may ascend and descend more than 2,400 m (8,000 ft) and race courses are generally far removed from hospitals. The course is often congested with both horses and runners, with the runners wearing standard road-racing attire and virtually no protective gear. Frequent mounting and dismounting stresses tack and a rider's skills. The stresses of riding competitively over difficult terrain are exacerbated by physical exhaustion from running on foot over half the distance of the race.

Methods

To better define the rate of injuries in the sport, I asked every applicant for the 1987 Park City (Utah) Ride and Tie to fill out a questionnaire detailing injuries suffered while training and while competing. An injury was defined as being severe enough to cause a loss of training time. Competitors were asked to list how many injuries they had sustained and whether the injuries had resulted from training or from competition. They were asked to describe their injuries and how they were sustained. Demographic details were also included in this survey. To follow up on these data, I interviewed by telephone the race directors of six well-recognized races, including the international championship. Details of any recalled accidents occurring over the past ten years were recorded.

Results

Only 32 of 60 competitors completed the questionnaire in full. The results are listed in Tables 1 and 2. The ages of competitors ranged from 15 to 55 with most being between 31 and 50. There were slightly more men than women. Most respondents were both experienced runners and riders. Of the 32 respondents, 26 stated that they trained at least 6 months and often 12 months per year. In training, most ran less than 64 km (40 mi) a week, and 9 of the 32 did most of the riding. This would suggest that one person, perhaps the owner of the horse, spent the most training time on horseback.

(Sayres WG Jr: Ride and tie—A hybrid sport with synergistic potential for injury. West J Med 1990 Sep; 153:319-321)

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A total of 14 competitors (44%) reported being injured severely enough during training to lose training time, with 9 (28%) listing more than one injury. Of the 32, 6 (19%) reported serious injuries sustained during competition. Because most teams compete only once or twice during the year, this would seem a high percentage. There was no difference between men and women in the number of injuries reported.

The 29 reported injuries included a skull fracture, a clavicle fracture, and two rib fractures. These accounted for a notable 13% of reported injuries. Superficial cuts and abrasions were the most commonly reported injuries. Others, primarily musculoskeletal, are listed in Table 2.

I also contacted by telephone the race directors of five popular ride-and-tie races. These races have been run from 5 to 15 times, with an average of 30 to 60 teams per race. The organizers of the international championship in Santa Cruz, California, were also contacted. At least ten highly competitive championship races have been held, with an average of more than 60 teams per race. Retrospective anecdotal data from approximately 49 races were available.

Few injuries were noted by the race directors, and these followed the pattern reported for horse-riding injuries in general: an open fracture of the tibia and fibula, a foot fracture, and four closed-head injuries, one of which required hospital admission. Three cases of heat exhaustion were reported. Organizers of races with a physician on hand reported more injuries than those with emergency medical technicians, suggesting a bias in reporting. Race directors' reports differed from anecdotal reports by competitors, who reported more frequent and more serious injuries.

TABLE 1.—*Experience and Injuries in Ride-and-Tie Competitors*

Experience, Training, and Injuries	*Race Competitors, No.*
Age, yr	
11-20	3
21-30	8
31-40	18
41-50	7
55	1
Sex	
Male	20
Female	12
Running experience, yr	
0-2	4
3-5	3
5-10	24
NA	2
Riding experience, yr	
0-2	5
3-5	4
5-10	19
NA	4
Training, mo	
0-2	1
3-5	4
≥6	26
NA	1
Weekly training, running, km (mi)	
≤48 (30)	13
50-64 (31-40)	10
66-80 (41-50)	7
>80	2
Weekly training, riding, km (mi)	
≤48 (30)	11
50-64 (31-40)	6
66-80 (41-50)	5
>80	9
NA	1
Training injuries, No.	
0	18
1	8
2-4	4
5-7	1
≥8	1
Competing injuries, No.	
0	26
1	3
2-4	3
5-7	0
≥8	0

NA = not answered

Discussion

Ride and tie can be seen as a hybrid of endurance riding and mountain running, both popular sports in the West. This survey shows that more serious injuries result from riding than from running. The three cases of heat exhaustion that were reported occurred on a low-altitude course in mid-August. In general, races are held in relatively cool mountain environments, where the risk of heat exhaustion is generally low.

The scientific literature associated with horse-riding injuries is devoted primarily to English-style riding, which includes hunter-jumper, dressage, and steeplechase riding. There is no published information on western-style riding, which includes "western pleasure," work-related riding, and some endurance riding. Riding techniques, tack, breeds of horses, terrain, and competitive activities all differ between western riding and its English counterpart. With few exceptions, ride-and-tie racers ride western, and therefore the results of existing studies to this sport must be applied with caution.

The severity of horse-related accidents is supported by data from the National Electronic Injury Surveillance System of the Consumer Safety Commission from 1979 to 1981: 105 horse-related deaths were reported from emergency departments across the country. Accounting for unreported cases, it was estimated that from 217 to 257 deaths may have occurred from equestrian accidents during that period. In 1979 alone there were an estimated 31,488 horse-related injuries leading to 3,558 hospital admissions.[1] In the 1973 to 1974 national hunt season in England, there were more than 237 recorded injuries, including 27 head injuries, 122 fractures, and 80 minor injuries.[2]

Head injuries consistently are the most severe of horse-

TABLE 2.—*Injuries Sustained in 32 Ride-and-Tie Competitors*

Injury	*Competitors, No.*
Skull fracture	1
Clavicle fracture	1
Rib fracture	2
Sprains	
Lower extremity	6
Back	4
Knee pain	5
Plantar fascitis	1
Superficial abrasions	9
Total	29

related injuries.[3,4] A ten-year review of death certificates in South Australia revealed 18 horse-related deaths, with 13 due to head injuries.[5] A one-year study in Sweden registered 174 patients, 66 of whom were younger than 15 years. Of these riders, 67% had head injuries, and 11% of the head injuries resulted in "cerebral injury." Of these patients, 27 reported persistent symptoms a year after the accident.[6] Head injuries were also found to be the most serious result of riding accidents in a two-year study of 8,768 patients with horse-related injuries at an Oxford, England, accident service.[7] Persistent symptoms from such accidents were shown in a British study of five National Hunt jockeys with posttraumatic encephalopathy.[2]

Wearing a helmet offers the most protection against head injuries from riding accidents. With the introduction of rules to ensure the use of approved helmets in Great Britain, the incidence of serious head injuries reported in one study was cut in half.[2] It is also well documented that riders frequently neglect to wear protective headgear. In another British study, half of head injury victims were not using helmets with safety straps.[8] In 110 horse-related injuries in Virginia, less than 20% of patients were wearing protective headgear. Only one of the head-injured riders was wearing a helmet.[9] Of 13 head injury-related deaths reported in South Australia, 9 of the victims were wearing no headgear.[5]

Western riders rarely wear helmets, and ride-and-tie competitors virtually never do.

Fractures emerge as another serious result of horse-related accidents. The rates of fractures ranged from 15% in horse show injuries[10] to 20% in a survey of United States Pony Club-related injuries,[11] to 35% in riding accidents in England,[7] 40% in fox-hunting accidents,[12] and 44% among riders in Sweden.[5]

Horse-related injuries do not appear to be related to the skill of the rider.[8,12] Studies have shown that many accidents occur in previously injured riders.[1,11,13] Swedish investigators reported that 35% of accident victims had had a previous history of injury.[6]

Competitors in ride and tie are subject to the same risks as those riders encountered in previous studies of horse-riding accidents—head injuries and fractures in particular. Although most injuries occur while training, the likelihood of injury is greatly increased during competition. Experience seems little related to accidents.

Although some respondents to my survey reported overuse injuries of the back and lower extremity, most injuries were related to the horse-riding aspect of the sport.

The use of protective headgear is the most obvious first step in preventing serious injuries in ride and tie. Because competitors run at least half the race, they may consider helmets cumbersome, but a quick-action buckle would allow for a rapid changing of the helmets during the ride while sacrificing little time. Without making wearing helmets a requirement of the race, however, it is unlikely that they will be used.

The diagnosis and treatment of head injuries has also emerged as a weakness in race coverage. After falling from the saddle not far from the start, a competitor at the national championships was allowed to finish the race but does not remember doing so.

The perception of the safety of ride-and-tie races varies notably from the competitor to the race director. Race directors reported far fewer injuries than did competitors. With this mistaken perspective that ride-and-tie races are actually safe competitions, race directors place little emphasis on preventing human injuries. While an ambulance usually stands by, riders are not required to wear protective clothing or helmets. Indeed, the horses and mules receive more medical attention than their human associates: at least two or three compulsory veterinary examinations are common in a competition.

Improved data collection, perhaps using the model of the US Pony Club, would allow for a better analysis of injuries and documentation of preventive measures. This may become possible with the formation of a national ride-and-tie association in 1988.

In comparison to English riding, ride and tie would seem to be in the early days of its evolution. Instituting good documentation and injury prevention would go far towards maintaining the health of its participants.

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Editorials

The Eosinophilia-Myalgia Syndrome

It is estimated that the eosinophilia-myalgia syndrome (EMS) has developed in more than 1,500 persons in the United States taking tryptophan (Centers for Disease Control, "hot-line" recording, May 1990). The experience acquired from clinical and epidemiologic studies indicates that EMS can be severe, disabling, and chronic, as described by the article by Criswell and Sack elsewhere in this issue of the journal.[1] Approximately 30% of affected persons have required admission to hospital, and at least 20 of these have died of causes directly related to the syndrome.[2]

The initial symptom in most patients is generalized myalgia of abrupt onset, sometimes severe enough to be virtually incapacitating and often accompanied by marked cutaneous hyperesthesia. Swelling of the extremities is also noted at this stage of the disease and is occasionally associated with weight gain. About half of patients have low-grade fever and self-limited respiratory symptoms with nonproductive cough and shortness of breath. During the acute phase of the illness, a variety of cutaneous lesions appear, either simultaneously or within a few days of the beginning of myalgia. These include areas of blotchy erythema on the extremities and chest, macular rashes on the trunk, purpuric lesions, and pruritus. Symmetric polyarthralgias are present in most patients but are not associated with morning stiffness or joint swelling. Following a fairly uniform acute syndrome, many patients evolve into a second phase of the illness that is characterized by the indolent and frequently progressive involvement of various organ systems.[3]

Scleroderma-like cutaneous changes are the most frequent and prominent chronic feature of the disease. Typically these are first noted on the lower extremities and are followed by involvement of the upper extremities and often of the trunk. In the majority of cases the digits and face are spared. The skin appears hyperpigmented and notably indurated, acquiring a woody consistency. Occasionally coarse dimpling (peau d'orange) and venous furrowing of the uplifted arm (groove sign) are observed. Raynaud's phenomenon, tendon friction rubs, telangiectasia, and ischemic digital ulcerations or nail-fold capillary changes, which are characteristic findings in patients with systemic sclerosis, are not present.

Full-thickness skin biopsies including the fascia and perimysium are necessary to document the full extent of cutaneous involvement. The characteristic histopathologic findings are thickening and severe fibrosis of the fascia, accompanied by inflammatory cell infiltration in the deeper layers of the dermis, the interlobular septa of the subcutaneous adipose tissue, and the fascia. Although lymphocytes usually predominate, plasma cells, intact and degranulating mast cells, and abundant eosinophils are also found. Local accumulation of eosinophil-derived proteins has been described.[4]

The severe myalgia of the acute phase may be followed by proximal symmetric muscle weakness. Serum lactate dehydrogenase and aldolase levels are almost invariably elevated, but the serum creatine kinase level is not and often is less than 10% of the upper limit of normal.[3] This dissociation between the levels of creatine kinase and aldolase was also noted in several patients described by Criswell and Sack.[1] Electromyographic studies occasionally show evidence of acute denervation or a myopathic pattern but can be normal even in patients who have clinically apparent muscle weakness.

Histopathologic examination of muscle biopsy specimens shows prominent perivascular and interstitial inflammatory infiltrates with mononuclear cells, plasma cells, rare eosinophils, and increased connective tissue in the perimysium and endomysium. Vasculitis, however, is notoriously absent. Severe neurogenic myofibrillar atrophy and evidence of regeneration have also been described in severely affected patients.

Sensory and motor neuropathy is the most serious late complication of the eosinophilia-myalgia syndrome. Histopathologic and histochemical examination of nerve biopsy specimens has shown severe axonal degeneration and focal mononuclear infiltrates around epineural blood vessels.

The pulmonary symptoms frequently noted in the early phase of the illness are usually self-limited, but dyspnea may persist and in some cases progress. Radiologic studies have shown diffuse interstitial infiltrates and pleural effusions in some patients but are normal in others despite clinical evidence of lung involvement. In contrast, pulmonary function may be abnormal even in patients without respiratory symptoms, and a severe reduction in the carbon monoxide diffusing capacity is not uncommon. Evidence of parenchymal inflammation has been found on specimens of transbronchial biopsy or bronchoalveolar lavage. Severe pulmonary hypertension, as noted in one of the patients of Criswell and Sack,[1] has been observed in several patients as a late sequel.

Cardiac involvement has been described, including conduction abnormalities, right ventricular strain, and cor pulmonale with tricuspid regurgitation following the rapid development of pulmonary hypertension.

Although peripheral blood eosinophilia is one of the criteria required for the diagnosis of EMS,[3] it is becoming apparent that some patients with the syndrome lack an elevated eosinophil count, as pointed out by Criswell and Sack.[1] Caution should be exercised, however, in diagnosing EMS in patients without eosinophilia, as many features of the syndrome may be mimicked by a variety of rheumatic diseases including systemic sclerosis, polymyalgia rheumatica, and fibrositis.

The clinical course of EMS is variable. Some of the early symptoms are self-limited and resolve within a few weeks. The discontinuation of tryptophan usually does not result in an appreciable change in clinical symptoms or in a consistent fall in the eosinophil count. The initial response to glucocorticoid therapy is favorable in a majority of cases, resulting in an improved sense of well-being, decreased myalgia and arthralgia, and a reduction of limb edema, accompanied by a prompt normalization of blood eosinophil and serum aldolase levels. Following the initial favorable response, however, a subset of patients experience no further improvement or show a progression of symptoms. Identifying and characterizing this group of steroid-resistant patients remains one of the major challenges for physicians caring for patients with EMS.

The pathogenesis of EMS is not well understood at this time, and several possible mechanisms have been postulated. Peripheral blood eosinophilia is characteristic of a number of allergic and autoimmune diseases. The coexistence of peripheral blood eosinophilia and cutaneous changes suggests a relationship to the syndrome of diffuse

fasciitis with eosinophilia (Shulman's syndrome), which is characterized by clinical and histopathologic alterations of the integument indistinguishable from those found in EMS.[5] Shulman's syndrome, however, is not associated with either the multisystem involvement or the presence of antinuclear antibodies frequently encountered in EMS.

Because of the persistent eosinophilia, a relation of EMS to the idiopathic hypereosinophilic syndromes, a group of chronic diseases characterized by eosinophilic infiltration of the skin and various internal organs, has been suggested. In similarity with EMS, peripheral neuropathy, myositis, skin rash, endocardial fibrosis, and pulmonary infiltrates are common in this group of diseases.[6]

The eosinophilia-myalgia syndrome also resembles clinically and histopathologically the toxic epidemic syndrome, a multisystem disease associated with the ingesting of adulterated cooking oil that occurred in Spain in 1981.[7] A common pathogenetic mechanism for these two disorders has been postulated (see below).

The role of tryptophan in the pathogenesis of EMS is not clear. Abnormalities in tryptophan metabolism have been suspected to play a role in various fibrotic diseases[8] and have been shown in some patients with EMS.[9] Tryptophan, however, had been commonly used in the United States for more than a decade before the epidemic occurrence of EMS, suggesting that a contaminant(s) in the preparation rather than the amino acid may be the causative agent. Extensive studies to identify such contaminant(s) have not been conclusive to date. The possibility that aniline-related compounds may be involved in EMS has been suggested[10] because aniline derivatives that have been implicated in the pathogenesis of the toxic oil syndrome are used in the production of tryptophan.

The dramatic increase in peripheral blood eosinophils and their conspicuous presence in affected tissues suggest an important role for these cells in the development of the tissue damage of EMS. Eosinophils release a variety of toxic granule-associated proteins that have been shown to be present in affected tissues and are elevated in the blood of patients with the syndrome.[4]

As discussed in detail by Criswell and Sack,[1] the presence of inflammatory cells in affected tissues in EMS suggests that these cells or their products may play a role in the pathologic manifestations of EMS. For example, degranulating mast cells are found in skin biopsy specimens of patients with early progressive cutaneous disease. Mast cell products interact with eosinophils and dermal fibroblasts and may stimulate the synthesis of extracellular matrix components, resulting in the development of fibrosis.[11] We have recently demonstrated the widespread activation of collagen gene expression in EMS dermal fibroblasts employing in situ hybridizations with human complementary DNA.[12] Furthermore, transforming growth factor-β_1 (TGFβ_1), one of the most potent signals to stimulate collagen production, has been shown to be present in fibroblasts and inflammatory cells in affected tissue (S.A.J. and collaborators, unpublished observations).

Although cytokine-fibroblast interactions may play a major role in the development of EMS, the complex clinical characteristics of the syndrome and the variety of systems affected suggest that several factors may be involved in its pathogenesis. For example, peripheral nerve damage may be a toxic effect mediated by tryptophan metabolites, contaminants of the tryptophan preparations, or the toxic substances released from eosinophils. On the other hand, the cutaneous and visceral fibrosis may be related to the activation of T lymphocytes with the release of fibrogenic lymphokines such as TGFβ_1 or to degranulation of mast cells with subsequent activation of fibroblasts. Understanding the mechanisms that result in the development of the various pathologic alterations of EMS should provide new insights into the pathogenesis of fibrotic diseases and may lead to the development of novel forms of therapy for these frequently crippling diseases.

This work is supported in part by grant No. AR 19101 from the National Institutes of Health.

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Hemochromatosis—Treatment Is Easy, Diagnosis Hard

HEMOCHROMATOSIS HAS BEEN RECOGNIZED for about 40 years as an iron storage disease that could be arrested or reversed by iron removal through phlebotomy. The problem has been not with the treatment but with the recognition of the condition. The diagnostic triad of hepatomegaly, pigmentation of the skin, and diabetes mellitus was rarely seen. Laboratory tests for its detection were limited. In addition, its separation from a number of other iron-loading conditions was difficult.

The situation has gradually changed in the past two decades. The course of the disease is now better defined. Hemochromatosis is a genetic disorder, the hallmark of which is excessive iron absorption. There is an additional failure of reticuloendothelial iron storage during the initial stage, resulting in the localization of the excess iron in the parenchymal cells of the liver. For many years there may be no tissue damage; then minor evidence of liver dysfunction may appear—the serum alanine aminotransferase (previously serum glutamic-pyruvate transaminase) liver function test being the most sensitive—and iron spills over into other parenchymal tissues. Initial symptoms are highly variable from patient to patient, but eventually the symptom complex expands into a more recognizable form.

The availability of laboratory measurements of plasma iron and iron-binding protein from which transferrin saturation could be calculated, the development of the plasma ferritin measurement, and a better understanding of the interpretation of these two screening tests have helped the diagnostic approach immeasurably. The recognition of the close relation between the hemochromatosis gene abnormality and the HLA complex has provided insight into the genetics of the disorder and has improved the diagnosis among siblings of a proband with the disease. Then, too, there is now a more detailed knowledge of the symptoms produced by parenchymal iron overload. Observations in the past decade place emphasis on gonadal failure and arthritis of the metacarpophalangeal joints of the second finger as early manifestations. It should also be appreciated that the presenting symptoms are modified by the rate of iron accumulation and the patient's age at the onset of symptoms. For example, gonadal and cardiac failure are particularly prominent in patients presenting with symptoms in their 20s and 30s. This is consistent with presenting symptoms in the more rapid iron loading of thalassemia and sideroblastic anemia.

How common is hemochromatosis? Most practicing physicians have never recognized the disease in their practice. The best information suggests that one person in a few hundred may have the homozygous form of the disorder and therefore may have the potential of sufficient iron overload occurring to produce tissue damage. A nearly tenfold difference exists between these prevalence studies, which include the preclinical disorder, and the number of cases diagnosed clinically. Does this mean that we are missing the diagnosis nine times out of ten?

There are undoubtedly several reasons for the disparity. Prevalence data are sparse. Much of our information may come from populations of high gene concentration that have evoked a special interest in the disease. Studies using screening tests on "unprejudiced," predominantly white populations are far more limited but suggest a lower prevalence of affected persons, perhaps 1 per 1,000. Another explanation is the discrepancy between the condition and its symptomatic state. We know that the genetic frequency is equal in men and women, yet symptomatic disease in women occurs only about a fifth as frequently as in men. In other words, four of five women do not accrue sufficient iron to be symptomatic. There is also a proportion of men who go through life without symptoms; others have symptoms that are so mild or nonspecific that the disorder is not recognized on clinical grounds. The final possibility is that physicians are not sufficiently astute in making the proper diagnosis. All of these elements undoubtedly explain the apparent discrepancy between reported prevalence and actual diagnosis.

Since the number of practicing physicians approximates the number of symptomatic patients with hemochromatosis, the average physician will rarely, if ever, diagnose the condition. Yet even among the well informed, diagnosis is still a chancy matter because of the protean nature of presenting symptoms. At any rate, by the time recognizable symptoms appear, the "horse may be out of the barn."

In recent years the public has expressed its displeasure with this state of affairs. Lay societies have been formed whose mission is to disseminate information about the "bronze killer." Participants often are family and relatives of a patient whose unfortunate death was related to a delay or a failure of proper diagnosis. Their members are aware that the disease can be "cured" only if treatment is started before tissue damage occurs or that the disease can be arrested if recognized later on. Their information program has been so effective that people they reach are sometimes far better informed than their physicians.

How can disease detection be improved? In the silent years of the disorder, there is an accumulation of iron bound to the iron transport protein of the plasma, and hepatic iron stores become excessive. These changes may be detected by laboratory tests that are characteristic of, but not specific for, parenchymal iron overload. The earliest indicator is an elevation of plasma transferrin saturation, at first intermittent and then constant. This merely indicates an imbalance between the iron loading of this iron transport protein and its delivery of iron to transferrin receptors on cell surfaces. Such an elevation does not necessarily mean an increase in iron stores; it may be due to an abnormality in erythropoiesis, for example, caused by chloramphenicol ingestion or other types of marrow damage. It may be due to liver disease, to damage to a ferritin-rich tissue, or simply to an instability in plasma iron in a normal healthy person. Repeated determinations will settle this last point. Plasma ferritin is the other useful screening test; its level will increase progressively in an affected patient in proportion to the increase in storage iron to values of several thousand micrograms per liter. Values of as high as 2,000 μg per liter in the elderly are more frequently due to other forms of liver disease or to chronic inflammation such as rheumatoid arthritis. Values elevated for age and sex, however, when linked to an elevated transferrin saturation, merit more definitive evaluation for iron storage disease.

There are two points of attack on hemochromatosis. In the past the approach has been through the acumen of a practicing physician who, when faced with a patient whose symptoms suggest the disease, requests a liver biopsy. Difficulties persist in separating by biopsy the genetic disease from late-stage alcoholic or viral hepatic disease. In such patients the desferrioxamine iron excretion test may be helpful in separating the heavier iron load of idiopathic hemochromatosis; the test is only valid when cirrhosis is present. Quantitating hepatic iron from a liver biopsy specimen would be better, but a reliable iron determination on a fragment of tissue obtained by needle biopsy is not generally available.

Results to date indicate the limitations of this clinical approach, especially when the time of diagnosis is considered. The average patient's age at the time of diagnosis is older than 50 in a disorder that is assumed to begin its pathologic iron storage in childhood. Furthermore, after symptoms occur, there is an average lag period of about six years to diagnosis. It is hoped that a greater familiarity with the clinical features of the disease so beautifully presented by Smith in this issue of the journal[1] would reduce this interval. Because certain cellular damage, particularly that of the myocardium, is completely reversible, prompt institution of phlebotomy can be life-saving. Damage to other tissues may not be reversible, however. While physicians should be prepared to suspect hemochromatosis when appropriate symptoms are present, their "batting average" will continue to be predictably low until the disease is advanced.

The attack of the future will be preventing the disease by early detection of the disorder. Already, chance determinations of an elevated transferrin saturation or ferritin level have led to the detection of parenchymal iron loading in younger persons who show no evidence of tissue damage. It is in the preclinical years that a liver biopsy is uniquely diagnostic. There will be a generalized iron loading of parenchymal cells, but Kupffer's cells will be spared, and

there will be no evidence of cellular damage. At this stage, the marrow hemosiderin levels will not be increased. It is thought that such persons, once their iron stores are returned to normal and kept there, will have no medical effects of their genetic disorder.

A strong case can be made for incorporating measurements of the plasma iron, iron-binding capacity, and ferritin into the routine blood screen. A physician's role then will be to interpret these tests and to determine whether parenchymal iron overload is present. Without such a laboratory survey, there is little hope of recognizing hemochromatosis at the time when treatment has the greatest promise.

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Transcatheter Treatment of Congenital Heart Disease

Past, Present, and Future

SINCE THE 1950s, cardiac catheterization has been an important tool in the management of congenital or acquired heart disease. Over this 40-year span, changes have occurred not only in the techniques and equipment used to perform a cardiac catheterization in a child, but also over the past 10 years in the indications for cardiac catheterization. In the past, the primary reason for doing a cardiac catheterization was to make an anatomic or physiologic diagnosis. Although the advent of two-dimensional echocardiography and color-flow Doppler has in part replaced this indication, other new indications for cardiac catheterization in pediatric patients have emerged. Two of the major new indications include the following: electrophysiologic studies and therapeutic catheterization. Therapeutic catheterization can be divided into two major types: catheter-based interventions and pharmacologic intervention.

The vast majority of therapeutic catheterizations done in children involve catheter-based interventions. The report by Waldman and Swensson elsewhere in this issue clearly summarizes many of these catheter-based therapeutic procedures.[1] As the authors note, the birth of therapeutic catheterization can be traced to Dr William Rashkind's development of balloon atrial septostomy in the late 1960s.[2] The recent development of interventional pediatric cardiology, however, can be linked to two papers published in the early 1980s. Lock and co-workers reported their results in dilating experimentally created peripheral pulmonary artery stenosis in late 1981,[3] and about six months later, Kan and colleagues published their results on balloon valvuloplasty for the treatment of pulmonary stenosis.[4] Following these and other reports on the use of balloon angioplasty to treat various types of congenital heart disease, it became apparent that more information was needed regarding the techniques, complications, and safety of these new interventional procedures. Therefore, in 1983, pediatric cardiologists from a number of institutions formed the Valvuloplasty and Angiography of Congenital Anomalies (VACA) Registry.[5] More than 20 pediatric cardiology centers from around the world participated in this registry. The results of that registry have recently been published in the *American Journal of Cardiology*.[6-10] Based on that report and a number of other publications, including the current report of Waldman and Swensson, it is clear that balloon dilation is an effective, safe form of therapy for children with many forms of congenital heart disease, including valvar pulmonary, tricuspid, mitral, and aortic stenosis; coarctation of the aorta; peripheral pulmonary artery stenosis; and superior vena caval obstruction. There are, however, still a number of areas related to balloon angioplasty that need further evaluation. These include the following: long-term follow-up results, the use of these interventional techniques in infants, the socioeconomic benefits of these interventional techniques, and the combined use of interventional cardiology and cardiac surgery in the treatment of some forms of congenital heart disease.

To date, most of the data regarding the efficacy of angioplasty to treat congenital heart disease relate to initial or short-term—less than two years after angioplasty—hemodynamic studies. There have been no long-term studies—more than five years after intervention—that have documented that these interventional procedures provide long-lasting hemodynamic and angiographic correction of the congenital defect. To establish the efficacy of balloon angioplasty, these long-term studies will need to be done.

With regard to the use of these interventional techniques in infants, available data suggest that balloon valvuloplasty is safe and efficacious for the treatment of critical pulmonary stenosis in neonates. The use of balloon valvuloplasty to treat critical aortic stenosis in neonates is less clear, however.[11,12] Based on the findings of the VACA registry, valvuloplasty results in the same degree of aortic stenosis gradient reduction in children regardless of whether they are older or younger than 1 year. The incidence of significant complications, however, including death, aortic regurgitation, and femoral artery damage, is inversely related to the age of the child, with valvuloplasty performed during the first month of life having the highest rate of complications.[7] A major reason why infants and neonates have higher complication rates is thought to relate to the combination of the larger size (10 to 12 French) of the currently available valvuloplasty catheters and the relatively small size of infants' femoral vessels. In the future, with the development of new catheters with a smaller shaft size and lower balloon profile, valvuloplasty for aortic stenosis will be performed safely in most neonates and infants.

As well summarized by Waldman and Swensson, there are both major socioeconomic benefits and problems associated with interventional pediatric cardiology. The major benefits include shorter hospital stays, less need for blood transfusion, the lack of a surgical scar and the psychological trauma that entails, and the potential for large financial savings in an already overspent health care market. Major new problems that interventional cardiology has created include obtaining acceptance from third-party payers that these interventional procedures are no longer experimental and are therefore reimbursable; the need to regulate the indications for performing these procedures; the need to develop standards regarding accreditation for training pediatric cardiologists in these interventional procedures; and the need to establish guidelines for regulating which hospitals should be permitted to do these procedures.

The final area for which future research is needed relates to the interrelationship between interventional cardiology and cardiac surgery. In the past, before the use of a new interventional procedure was advocated, the catheter intervention was required to be able to replace surgical therapy as the treatment of choice; that is, the results of the intervention had to be as good or better than surgical treatment.

This is not the only way to judge the usefulness and merit of an interventional procedure, however. For example, at the University of Michigan we have been advocating the following approach to native coarctation of the aorta in children: If a child has a discrete isolated thoracic coarctation of the aorta, we recommend that balloon angioplasty be done as the initial procedure. If the angioplasty is unsuccessful (that is, if the resting systolic gradient between ascending and descending aortic pressures of more than 20 mm of mercury persists longer than three months after angioplasty, with or without upper extremity hypertension) then an operation is done. Using this approach, we have successfully and safely treated 55 children with coarctation of a native aorta (45 have required angioplasty alone and 10 have required angioplasty and subsequent surgical correction. In addition, there has been no increased operative morbidity in children who have had a previous angioplasty of a native aortic coarctation). Thus even though balloon angioplasty is effective in only 80% of children with native coarctation, there is still an important place for balloon angioplasty in the management of native coarctation of the aorta.[13]

Another example of the interrelationship between interventional cardiology and surgery occurs in children with pulmonary atresia, a ventricular septal defect, and multiple collateral vessels. In this lesion, neither catheter intervention alone nor surgical treatment alone is usually capable of adequately treating a patient. Catheter intervention is usually necessary to occlude collateral vessels and dilate stenotic peripheral pulmonary arteries, and surgical intervention is necessary to establish continuity between the right ventricle and pulmonary arteries and ultimately close the ventricular septal defects. In the future, more and more children with complex cardiovascular lesions will require the combined use of interventional cardiology and surgery.

In summary, over the past 40 years pediatric cardiologists have made remarkable progress in developing a nonsurgical method for treating various forms of congenital heart disease. With further modification of existing procedures, the validation of interventional procedures that are currently experimental—such as transcatheter closure of septal defects, transcatheter closure of patent ductus arteriosus, and the use of balloon expandable intravascular stents—and the development of even newer procedures, interventional catheterization alone or in combination with a surgical procedure will become the standard of care for the majority of children with congenital heart disease.

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Correspondence

Human Growth Hormone—Orphan With a Silver Spoon

To THE EDITOR: Douglas Frasier, a fellow pediatric endocrinologist, indicated that it was inappropriate to consider recombinant human growth hormone as a privileged "orphan" drug under the Orphan Drug Act because that allowed its exclusive producers, Genentech and Eli Lilly, to reap excessive profits.[1] Including this drug in the special orphan category was defended by representatives of Genentech and the Food and Drug Administration (FDA), successfully in my opinion. I agree that the availability of recombinant human growth hormone has proved beneficial and even life-saving in children with growth hormone deficiency. Not only does it prevent dwarfism, but it normalizes facial features and body configuration and prevents the severe hypoglycemia that can lead to brain damage. In view of the limited number of children with hypothalamic or hypopituitary growth deficiency, I think pharmaceutical companies deserve a good return for developing this product.

On the other hand, I am disturbed by efforts to push the use of recombinant growth hormone in children without growth hormone deficiency, including normal, healthy children with short stature and girls with Turner's syndrome. The potential financial bonanza here would make the $200 million profit estimates by Frasier appear to be small change.

We know the effects of excess growth hormone in humans with pituitary gigantism and acromegaly. Not only is height increment accelerated, but coarse thick features appear, there is enlargement of the hands and feet, and diabetes mellitus develops. Growth hormone in vitro increases the growth rate of many cells, raising the specter of neoplasia. Although the recent cases of leukemia in growth-hormone-treated children in Japan were not proved to be due to this treatment,[2] there is still cause for concern, in my mind, particularly in children with Turner's syndrome who have a chromosomal defect.

Genentech has made efforts to ensure the ethical use of its product by distributing it through pediatric endocrinologists. Recombinant human growth hormone is approved by the FDA only for use in growth hormone deficiency. There is now an application for FDA approval for its use in treating Turner's syndrome, however. There is pressure for its use in normal, short children from parents who have been led to think of it as a "height hormone" instead of a substance affecting many cells and metabolic systems.

Lately we have seen evidence here in northern California, the home of Genentech, that marketing people are beginning to prevail over the ethical medical scientists who previously were apparently in control. Pediatricians have been paid honoraria to attend free dinners in San Francisco to hear talks on growth hormone. The largest children's hospital in northern California had a "free growth screening day." Although the above events were sponsored by Genentech, the announcement gave no hint that Genentech was involved. A local Genentech representative mentioned that his income was linked to the amount of growth hormone prescribed in his territory. This same representative was involved in a "height screening program" in public schools in which the parents of short children were advised to see a physician concerning their child's height. A recent private newsletter mailed to all pediatric endocrinologists reported highlights of pediatric research meetings and clearly emphasized the viewpoints of Genentech investigators; the issue was produced by funding from Genentech.[3]

It could be argued that the above activities are simply aggressive marketing aimed at discovering undiagnosed growth hormone deficiency. In my mind, however, these activities are ethically questionable; they represent attempts to expand the use of growth hormone to persons without hormone deficiency and are inappropriate for a privileged orphan drug. In addition, I feel that the manufacturers should be required to show evidence that they are taking measures to prevent recombinant growth hormone from reaching the black market, where the drug is already being abused by athletes and others who can afford the high cost.

The opportunity for growth hormone to become a financial superstar lies in its use in short children without proved growth hormone deficiency (particularly in healthy short children), where its efficacy and long-term safety have not been shown. It is here that we can expect the most pressure to prescribe it, and there is disturbing evidence that few holds will be barred in attempting to reap the immense potential profits. Caveat emptor, FDA.

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Dr Sherman Responds

To THE EDITOR: I welcome the opportunity to respond to Dr Schoen's recent comments about the use of human growth hormone.

Genentech's Protropin (somatrem for injection) is currently indicated for the treatment of short stature associated with growth hormone inadequacy in children. Our commitment to the appropriate use of growth hormone replacement therapy extends to our continuing efforts at monitoring its use in clinical practice. Of the estimated 12,000 patients in the United States currently receiving the therapy, more than half are enrolled and followed in a Genentech-sponsored postmarketing study. The National Cooperative Growth Study was designed, among other things, to disclose unexpected adverse effects of growth hormone treatment. We have now accumulated almost five years of safety- and efficacy-related information in children treated with growth hormone. Treatment-related side effects are rare, and physical changes related to growth hormone excess in children treated with somatrem are essentially unheard of.

In addition, Genentech has in place a very reliable, controlled distribution system for somatrem. This unique distribution system was voluntarily put into place by Genentech, and we think it efficiently mitigates against misuse of the hormone.

Dr Schoen accepts growth hormone for the treatment of children with growth hormone insufficiency but questions its evaluation in other groups of children whose growth is retarded. When only pituitary growth hormone was availa-

ble, its limited supply effectively precluded its use or study beyond the treatment of only the most severely growth hormone-deficient children.

One of the benefits of recombinant DNA methods is that the supply of growth hormone now allows us to carry out controlled studies in other disorders associated with severe short stature such as Turner's syndrome or chronic renal insufficiency. We at Genentech believe that it is our responsibility to support research that may lead to treatments of medical conditions or diseases beyond the initial indication for growth hormone inadequacy. This research, in conjunction with the good judgment of prescribing pediatricians, may lead to improved quality of life for children afflicted with a variety of diseases.

Genentech also feels that it is important to develop educational programs that will bring the availability of therapy for all patients who need it. Increasing parent awareness of the existence of growth disorders could include height screening programs. As Dr Schoen accurately points out, the result of a height screening program may be a recommendation to parents of extremely short children to see a physician concerning their child's height. While some of these children may be diagnosed as having insufficient growth hormone secretion, others have been found to have a variety of medical disorders requiring attention and treatment.

Genentech takes pride in its innovative laboratory and clinical science, product development, and educational programs. We remain committed to bringing the best of biomedical science to patients who can benefit from our products and will continue to take steps to ensure the ethical use of growth hormone.

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A Profile of California's Physician Assistants

To THE EDITOR: Most of the 1,782 physician assistants (PAs) currently licensed to practice in California are graduates of the four in-state training programs begun in the early 1970s at Charles R. Drew School, University of Medicine and Science; Stanford University Medical Center; the University of Southern California; and the University of California at Davis.* In 1988 these programs collaborated in surveying their 1,263 graduates, using a mailed questionnaire, with telephone follow-up on a sample of initial nonrespondents. With data obtained from a majority of the graduates (641), the survey provides a reasonably representative profile of the backgrounds and the current roles of physician assistants in California health care.

About Their Backgrounds

The physician assistants surveyed had graduated between 1973 and 1987. Their ages in 1988 ranged from 25 to 63, with a median of 38. Over half (57%) were women. Most (58%) had entered training with a baccalaureate or higher degree. Clinical backgrounds varied, including nurses (30%), allied health (17%), corpsmen (16%), health aides (16%), and EMT/paramedics (9%). Nearly a third (30%) were of ethnic minority background, including 12% Hispanic, 11% African American, 3% Asian, 1% Native American, and 4% other. Most reported using a language other than English—usually Spanish—with their patients, and, notably, 34% of the total reported speaking Spanish with fluency.

Where They Practice

Most of the surveyed graduates are practicing in California (83%), with physician supervisors in primary care specialties (73%). Most work primarily in private physicians' offices (56%), with 14% in community clinics and 13% in county systems. Only 4% work primarily in urgent care or emergency departments, with 17% indicating hospital inpatient responsibilities. Almost half (45%) have more than one practice site, although most (87%) spend more than 70% of their time at their main site. Respondents reported having worked a mean of 3.7 years at their present main site, with an average current work week of 36.5 hours; 33% work more than 40 hours a week; 82% work more than 30 hours a week.

Types of Patients

The questionnaire asked for an estimate of the proportion of several types of patients seen in the respondent's "most recent week of regular practice." Estimated practice proportions exceeding 15% are interpreted here to indicate substantial involvement with a given category of patients. Using this measurement, 32% reported more than 15% of their practice involved patients not fluent in English, 61% reported more than 15% of their practice being with patients of ethnic minorities, 46% with patients on Medi-Cal, and 22% with patients whose care was unreimbursed. The same level of substantial involvement was reported for pa-

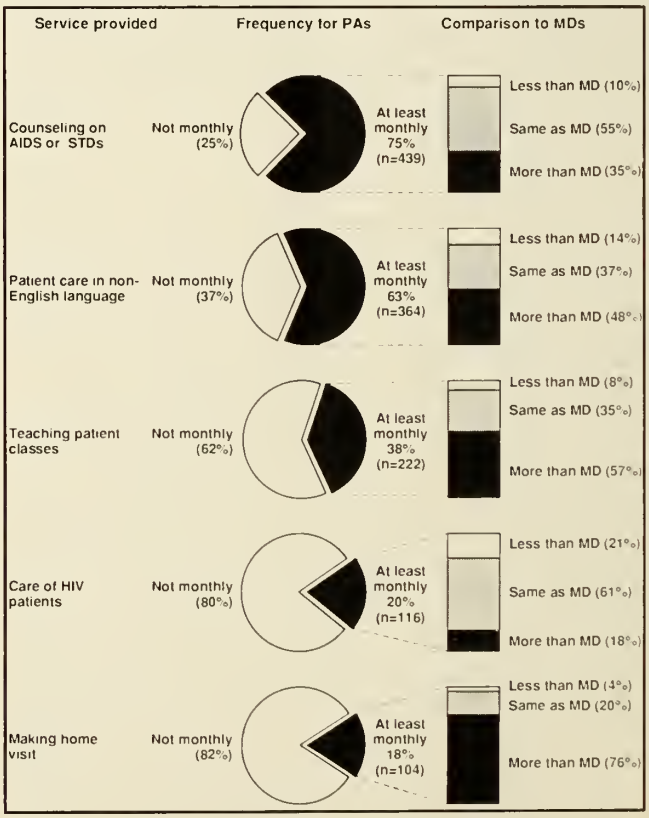

Figure 1.—Frequency of selected services provided at least monthly by physician assistants compared with their physician supervisors is shown.

*The work reported here represents a collaborative effort with Jack Liskin, PA, Director, USC/PA Program; Correne Treguboff, FNP, MHS (deceased), UC Davis FNP/PA Program; William Burnett, Principal Consultant, California Health Manpower Policy Commission; Wendell Wharton, PA, Director, Charles R. Drew Medex PA Program; Janet Mentink, FNP, MHS, Acting Director, UC Davis FNP/PA Program.

tients over 65 years of age by 33%, for children under five years of age by 34%.

Distinctive Features About Their Practices

The questionnaire asked about the types and frequency of tasks performed by physician assistants. "Regular" tasks were performed one or more times per month. Physician assistants were also asked to compare their frequency of providing services with the frequency of service provided by the principal physician supervisor. Figure 1 summarizes responses of particular interest.

Discussion

California physician assistants have entered training from a variety of backgrounds. Most already have a baccalaureate degree. Clinical training, then, builds upon diverse sets of knowledge, skills, and social experiences.

Of special note, in view of California's growing minority populations, is the large representation of ethnic minorities in the profession. The fact that most use another language with some of their patients, many with fluency, suggests that physician assistants are likely contributing to improved access to care for underserved minority patients. It is quite possible that such care may be culturally attuned to minority concerns as well.

Physician assistants are realizing goals set out for the profession by the state legislature in that most graduates practice in California and work with physicians in the primary care specialties. They also frequently work in settings such as community clinics and county systems that care for the medically disenfranchised. Their self-reported involvement with patients on Medi-Cal and those without reimbursement for care suggests that they are playing substantial roles with the medically underserved.

Role delegation between physician assistants and physicians varies greatly among practices. The data summarized in Figure 1 suggest that physician assistants commonly complement as well as extend the services provided by their physician supervisors/colleagues.

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Family Physicians and Obstetrics

To THE EDITOR: The article by Pyskoty and colleagues, "Malpractice Litigation as a Factor in Choosing a Medical Specialty," in the March 1990 issue[1] was an important contribution to our understanding of the process that may affect some of the current physician maldistribution in the health care system. Studies suggest that less than 11% of University of Illinois students choose family practice each year.[2] Having recently examined several of the Chicago programs, I found that family medicine is a relative "blind spot" for many of the medical schools there.

In the high risk-low risk dichotomy, family practice was placed in the low risk group. Training in obstetrics remains as one of the important parts for accreditation of a family practice program by the Residency Review Committee. The American Academy of Family Physicians 1989 Congress of Delegates reaffirmed the place of family physicians in the delivery of obstetrical services.[3] This is particularly important for rural and underserved groups. Projected cost for liability insurance affects specialty choice by discouraging medical students who fear legal and financial risk. This effect is unique for the specialty of family practice, which covers many areas of subspecialty endeavor, including obstetrics. Our studies and others' have documented the dramatic effect of liability insurance on family practice.[4-6]

Tragically, students' perception of insurance costs are frequently inaccurate or misleading, or both. Some students routinely overestimated family practice insurance costs by 200% to 400%. There is an unfortunate influence on specialty choice.[4,5]

As family physician role models disappear from training environments and the technical imperative marches on, cesarean section rates are almost 25% nationally. The American College of Obstetrics and Gynecology has declared that a physician cannot perform induction of labor without cesarean section capability. These events, which are at least partially attributable to the liability insurance environment, uniquely affect the specialty of family practice.[7]

In the same issue of the journal, Midtling and co-authors point out the systematic underfunding of family medicine residencies.[8] Ironically, training for obstetrical skills is a labor-intensive task.

Pyskoty and colleagues' study is an interesting one with an excellent discussion. In terms of one of the primary care specialties, family practice, the high risk-low risk dichotomy is misleading. Insurance concerns and the role of obstetrics within the specialty are powerful forces that partly contribute to the crisis in rural and underserved health care.

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Dr Charles Responds

To THE EDITOR: I appreciate very much Dr Rodney's thoughtful comments on our article.[1]

The reference to our high and low risk dichotomy with family practice included as low risk is of interest. As readers may have noted in our article, this designation was based on the rate classification used by the Illinois State Medical Inter-Insurance Exchange, which is the physician-owned insurer associated with the Illinois State Medical Society. How many of those family practitioners in the low risk insurer classification actually engage in obstetrical care is unknown to us. Based on our knowledge of students at the University of Illinois at Chicago, our students perceive family practice primarily as an outpatient discipline and would

not expect to perform obstetrical services as part of that practice in most areas of Illinois. This may indeed be a sad commentary on the current climate of practice and, as Dr Rodney points out, especially for rural and underserved groups.

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Just Say No?

To THE EDITOR: In "The New Disease Model of Alcoholism" in the May issue,[1] Dr Wallace cites studies indicating that some people are genetically predisposed to drink alcohol and that some people are genetically predisposed to be harmed by alcohol. "Studies of drugs other than alcohol," he says, "have shown similar results." Given these genetic predispositions, "and a psychosocial environment that encourages repeated exposure to alcohol, illness predictably results." He concludes that if its devastating effects are to be stopped, alcoholism must be understood, according to the "new disease model," as a "biopsychosocial disease," "rather than a problem of will-power, character, or morality."

Genetic predispositions—although interesting—are at present therapeutically irrelevant. What successes we see in prevention and treatment rely for the most part on addiction being addressed—in contradistinction to Dr Wallace's view—as a problem of personal responsibility and fortitude. Some people who are at apparently high familial and psychosocial risk never become addicted. Are they not to be credited for having made good, tough, responsible decisions? Some people, after years of hard-core addiction, "just say no"—sometimes by virtue of their own resolution and sometimes in connection with groups such as Alcoholics Anonymous. In the absence of effective disease model interventions, helpers addressing the problem of addiction must try to reinforce the very qualities that Dr Wallace repudiates.

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* * *

Dr Wallace Responds

To THE EDITOR: Dr Goldstein has raised several important issues in his letter. With regard to therapeutic applications of research on genetic predispositions to alcoholism, there are several things to bear in mind. While biomedical applications are not yet available, patients do benefit from cognitive uses of this material. Many patients entering treatment for alcoholism suffer from irrational guilt and self-blaming. Guilt of this nature and self-blaming are associated with continued relapse and not stable recovery. We find it useful to teach patients that while they are not to blame for developing the disease of alcoholism, they are indeed responsible for doing something about it.

It is true, as Dr Goldstein has pointed out, some people who are apparently at high familial and psychosocial risk do not become addicted. We do not know, however, how many such persons exist, nor do we know the factors that enable them to escape addiction. Without question, such persons are deserving of close scientific study.

Dr Goldstein sees more of a role for will-power, personal resolutions, and morality in the treatment of addictions than I do. Advising people caught in the throes of addiction to alcohol and other drugs to "just say no" is rather like telling the schizophrenic to just stop hallucinating, urging the bipolar patient to just calm down, and asking the severe affective disorder patient to cheer up. Alcoholics Anonymous (AA) does not urge people to "just say no," as Dr Goldstein states. Alcoholics Anonymous suggests that alcoholics must first admit that they have become powerless over alcohol and that their lives have become unmanageable. Paradoxically, it is in the admission of powerlessness over alcohol that AA people gain access to other sources of power over the disease of alcoholism and not "by virtue of their own resolution."

Finally, the recent research on genetics and brain chemistry serves to remind us that alcoholics have been stigmatized too long as people of weak will, flawed character, and low morals. Alcoholics are not weak people trying to be strong people. Nor are they bad people trying to be good people. They are ill people trying to get well.

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Physician Diversion Programs and AA

To THE EDITOR: In "Diversion Programs for Impaired Physicians" in the May issue,[1] it is obvious that Chet Pelton and the California Diversion Program embrace Alcoholics Anonymous (AA) as their recovery tool. Indeed, in diversion, AA is literally synonymous with recovery. Physicians who find themselves subjects of the diversion program are expected to embrace AA and work the 12 steps of AA. Chet Pelton states that to complete the program "physicians must demonstrate a life-style that will support sobriety for the rest of their lives." He means AA.

Anyone who is familiar with AA and the 12 steps will be aware of its religious nature. We are expected to "turn our will and lives over to God. . ." and through "prayer and meditation improve our conscious contact with God. . ." The AA "big book" says "without help it is too much for us. But there is One who has all power—that One is God. May you find Him now!"

Those of us, nonbelievers, who do not subscribe to magical thinking and irrational beliefs have this AA "religion" forced upon us by a government agency! Chet Pelton, his compliance officers, and members of the drug evaluation committees are, as a rule, recovering persons who have fully embraced the AA doctrine. Their lives and livelihoods depend on AA. At my first encounter with a drug evaluation committee, a physician member jumped to his feet and cursed at me after I made a remark that was critical of AA.

There are secular alternatives to AA—secular sobriety groups are starting up in many large cities—but many AA members are openly hostile to these, viewing them as a threat to AA. According to AA belief, God is the only one who can make one whole, and building a "spiritual program" and having a personal relationship with God is the only thing that can keep one sober. These people are very skeptical that an atheist can stay sober. A sober atheist is a threat to their own belief system.

The California Diversion Program has a 72% success rate because the physicians attend group discussions where they can work out their problems, they are monitored with

frequent urine testing, and their licenses are being held for ransom to ensure compliance. The raw success rate for alcoholics who attempt to recover just by attending AA meetings is a dismal 20% or less.

Dr Joseph Frawley of the Schick-Shadel Institute reports that 60% of the Institute's patients are agnostics or atheists compared to less than 30% of those admitted to AA role programs. Yet Schick's program boasts a recovery rate as high as traditional programs without reliance on AA.

Most nonbelievers who seek recovery at AA must change their beliefs or tolerate the constant barrage of religious rhetoric. Many end up leaving, possibly to die from their disease.

In the California Diversion Program nonbelievers cannot leave because their licenses are at stake. They are subject to critical review by authorities who equate recovery with Alcoholics Anonymous.

GILBERT ANDERSEN, MD
515 E Oceon, Suite E
Lompoc, CA 93436

REFERENCE

1. Ikeda R, Pelton C: Diversion programs for impaired physicians, *In* Addiction Medicine (Special Issue). West J Med 1990 May; 152:617-621

* * *

Mr Pelton Responds

To THE EDITOR: Dr Andersen's letter is generally correct. We do embrace AA and the 12 steps of AA. Our experience is that most physicians who develop a strong recovery program have embraced AA.

There are some physicians, however, who are not able to embrace AA. Some physicians, and others as well, have difficulty discovering the distinction between a Higher Power and God. Most physicians are able to identify with the spirituality of a Higher Power rather than the religious aspects of God.

For those physicians who do not believe in God or who cannot relate to a Higher Power, we suggest other meetings such as secular sobriety groups. If the message of sobriety comes through in those meetings, that is where the physician should go.

CHET PELTON
Diversion Progrom Monoger
Medicol Boord of Californio
1434 Howe Ave, Suite 84
Socromento, CA 95825

There Ought To Be a Law

To THE EDITOR: I read with interest and pleasure the May 1990 issue on *Addiction Medicine.* As a former long-time member of the Medical Board of California, I would like to make some additional comments about the problems of prescription drug abuse[1] and the impaired physician.[2]

With regard to the "duped" physician, I agree with Wesson and Smith that the physician receives too much blame. As a family practitioner, it is not uncommon to be caught in the bind of wanting to minister to someone's pain while suspecting that a hustle is going on. It is often necessary to rigidly limit pain prescriptions, but this leaves bonafide problems untreated. A sensitive physician is often in conflict over this issue. In my opinion it would be helpful if the Board and the California Medical Association would jointly sponsor legislation making it a felony to seek a controlled substance from a licensed prescriber under false pretenses. I do not know of such a law now, and I think it would have a deterring effect on many of the hustlers, most of whom seem to be more middle class and educated than other abusers.

Finally, I think California's impaired physician program deserves the greatest praise for its accomplishments. I do not think the article was detailed enough in pointing out the great amount of integrity and professionalism involved in running a confidential treatment program within a law enforcement agency. This was able to be accomplished under the magnificient leadership of the Board's former chief medical consultant Dr Joseph Cosentino, who recently passed away.

JEOFFRY B. GORDON, MD, MPH
4747 Mission Blvd, Suite 4
San Diego, CA 92109

REFERENCES

1. Wesson DR, Smith DE: Prescription drug abuse—Patient, physician, and cultural responsibilities, *In* Addiction Medicine (Special Issue). West J Med 1990 May; 152:613-616
2. Ikeda R, Pelton C: Diversion programs for impaired physicians, *In* Addiction Medicine (Special Issue). West J Med 1990 May; 152:617-621

CORRECTIONS

The authors have discovered an error in their case report of "Acute Oleander Poisoning—A Suicide Attempt in a Geriatric Patient."[1] The legend for Figure 1, which read "Digoxin serum concentration versus time, in minutes, is shown," should have read "Digoxin serum concentration versus time, in hours, is shown," and the X axis of the graph also should have been labeled "Time, hours."

REFERENCE

1. Driggers DA, Solbrig R, Steiner JD, et al: Acute oleander poisoning—A suicide attempt in a geriatric patient. West J Med 1989 Dec; 151:660-662

* * *

On page 35 of Jenkins et al,[1] the percentage of Vietnamese refugee women who had never had a Papanicolaou test should be 85%, not 89%. The percentage shown in Table 2 is correct. The authors and the journal staff apologize for any confusion caused by this error.

REFERENCE

1. Jenkins CNH, McPhee SJ, Bird JA, et al: Cancer risks and prevention practices among Vietnamese refugees. West J Med 1990 Jul; 153:34-39

Lessons From the Practice

Dying of a Broken Heart

GENE W. MASON, MD, *Lake Stevens, Washington*

My half-awake brain perceives the taste of thin air and the sound of labored breathing. Surely I am at altitude again, but where is the cool caress of glacial breeze? The exhaustion of altitude is there, but where is the smell of heather and tiny wildflowers? My ears are filled with the dry hacking cough of the high mountain regions, but there is no sound of wind or flapping tent. I awaken with the exaggerated breathing following the cessation of breathing, characteristic of high altitude sleep but also characteristic of chronic heart failure. My eyes open to a bare white hospital room rather than an orange mountain tent. I am approaching the end point in the longest, most grueling adventure of all.

The adventure started four years ago when I suffered a large myocardial infarction. The horror and surprise were simultaneous since little about me fit the typical candidate. Not only had I spent a considerable part of my life involved in mountaineering, but I was a nonsmoker who was never obese, diabetic, or hypertensive. My cholesterol level the day of the infarct was about 150.

The phrase "suffered an infarct" marked only the beginning of the suffering. Since that event, there have been 27 hospital stays for acute heart failure, pulmonary edema, life-threatening arrhythmias, intractable angina, or some combination thereof. During this time I underwent 13 electrical cardioversions, 8 coronary angiographies, 5 angioplasties, 6 heart catheterizations, 1 pacemaker insertion, and a triple coronary bypass.

But, still, I have difficulty getting the hang of it—being a cardiac cripple, that is. I forget to take my disabled sign with me in the car. My wife says I don't complain enough. People think I move too well—they don't see me huffing and hurting secretly around the next corner. Even my cardiologist says, "You look too damned good."

There are several reasons why I look healthy. Except for a failing heart, I am. In addition, many people say I never would have survived this long except for an incredible zest for life. Maybe this helps me present an appearance of health. But, more important, I'm a pretty good actor. Being ill is an embarrassment to me, so I act well and go hide from people when I feel too "poorly" to play the role. Finally, there's the stubbornness—I refuse to be cowed by my disability. Wonderful words, but I'm often cowed anyway.

To some degree, I have learned to cope. Conservation of effort has become a way of life, the shortest distance between two points, a ritual. Think ahead; never make two trips when one can do. Never carry nonessentials. Don't stand when you can lean against something, and don't lean when you can sit. Eat slowly. Since you can't swallow and breathe simultaneously, rapid eating causes shortness of breath. Too much talking does the same. Zealously meter what little energy you have. Live a life in slow motion.

There's the bitter acceptance of helplessness. No longer do I have the physical capability of defending myself or others against hostile elements, be they animate or inanimate. No longer can I run off a dog, go for help, change a flat tire, chase anybody or anything, or even run away. I cross streets very carefully, knowing I can't move fast enough to evade any vehicle. It's all part of the gradually diminishing self, an alternate version of "The Incredible Shrinking Man." It becomes very difficult to maintain feelings of self-worth.

Last spring I was diagnosed as "approaching end-stage, dilated, ischemic cardiomyopathy." It was no longer sufficient to cope with continuous disability. There was the necessity of coming to grips with death.

This produced new feelings. There was a lack of interest in purchasing personal items, particularly clothes. My possessions will last me a lifetime. A year? Two? My mind made a short list of things to accomplish before death, and I found myself arguing with some inner being that I couldn't die until the list was completed. There's a greater appreciation of nature. My eyes linger longer while looking at flowers, trees, birds, clouds—as I may never see them again—images I want to record forever.

I think a lot about other people. Although I envy the multitudes with healthy hearts, I have no desire to secretly pluck one from anyone, even if it were possible. I'm filled, however, with fanciful wishes about seizing one that is no longer needed, be it because of accident, suicide, or execution. I'm chagrined by the waste of perfect hearts. But, also, I find myself envying those who've died a quick death. It's exceedingly difficult to die over months and years and see myself ever so slowly diminish.

For a long time, my answer to the frequent question, "How are you?" was "Fine." In recent months I could no longer allow myself that deception and changed my answer to "hanging in there," which is just what I'm doing: hanging in there, trying to maintain a somewhat miserable and fragile status quo.

The nights have become different. In the quiet darkness, I become more aware of my beating heart and how I really feel. Wakefulness becomes a regular part of each night. There are guilt feelings for making life so difficult and unknown for my wife and family. They try so hard to be understanding, but nobody can really understand. I grieve over some of the missed family events—graduations, trips, vacations. I try to dwell on what I can still do, rather than on what I cannot. It's a frustrated reassurance.

Often my mind churns with thoughts of, "Why me? How could I have avoided this? What could I have done differently?" And then there's the lingering suspicion that my own heart has turned weak and traitorous.

For a long time, a strange idea has frequented my rever-

(Mason GW: Dying of a broken heart. West J Med 1990 Sep; 153:332-333)

Dr Mason practiced anesthesiology in Everett, Washington. He now lives in Lake Stevens, Washington.
Reprint requests to Gene W. Mason, MD, 607 Shore Rd, Lake Stevens, WA 98258.

ies, a feeling that if I could somehow escape my present surroundings, I could escape my illness. If I could sneak away, move to a remote location, take a different name, hide out, I could elude past and illness alike.

Some nights I dream of running long distances through the woods, across fields, and up and down valleys. Oh, the joy of it. I awaken to an erratically pounding heart and the reality that I haven't been able to run in four years. More recently, my angina and breathlessness are even carried into my dreams.

Now a new dream has entered my life; hope has been revived. There is the promise of a new heart and 70% chance of survival for five years—a chance to reverse the diminishing process. While waiting and hoping to be accepted as a candidate for this almost-unbelievable miracle, I had to consider the prospect of being rejected, as the vast majority are. I salved those anxieties by telling myself that perhaps I could somehow survive without a new heart, that I would improve in spite of the medical predictions, that I could adapt to a lesser life with my own heart. But could I ignore the suffocating feeling of congested lungs or the indescribable, intolerable, urgent aching of angina? Unfortunately, wishful thinking plays a limited role in life.

The prospect of a transplanted heart brings new thoughts to mind, thoughts of some healthy young stranger who has no idea that our lives will intersect. What is he or she doing today? What kind of life is it? And, finally, the big question: Will our lives intersect at all before I diminish to nothingness? About 30% of people awaiting transplanted hearts die before one becomes available. It's a strange and macabre race.

The concept of a new heart—accepting a living thing to be intimately woven into my life, protected and nurtured, to marvel at its growing strength, adapting, becoming a key member of my family of organs—to me, is somewhat analogous to adopting a child. I'll certainly give it a good home.

February 4, 1990

Editor's Note:

Dr Mason received a heart transplant on March 28, 1990, at Stanford University. His recovery has been excellent, he reports, and he returned to his home in Washington State at the end of May. He is on high-dose immunosuppressant therapy and has to guard against potential infections, but, in general, he is leading a normal life—walking at a brisk pace and bicycling. There are side effects to the medication, he says, but, as with many heart patients, he considers himself so lucky that to complain would be demeaning.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
STEPHEN J. McPHEE, MD
Series' Editors

THE WESTERN JOURNAL OF MEDICINE

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Submitting Manuscripts

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In view of *The Copyright Revision Act of 1976*, transmittal letters should contain the following language: "In consideration for reviewing and editing my submission, the author(s) undersigned hereby transfers, assigns, or otherwise conveys all copyright ownership to THE WESTERN JOURNAL OF MEDICINE in the event that such work is published by the journal." This statement should be signed by *all* authors.

Authors are urged to seek clarity and succinctness in all manuscripts regardless of subject matter or format and to give close attention to syntax, grammar, and spelling.

Preparing Manuscripts

The original manuscript and *two* copies should be submitted on heavy bond paper (8½ by 11 inches, *not* erasable), typed *double-spaced throughout* (including legends, tables, and references) on one side of the paper, with 1½-inch margins. Articles should not exceed 3,000 words (less than 15 text pages typed double-spaced). Under exceptional circumstances only will articles longer than 4,000 words be published. Pages should be numbered consecutively, beginning with the title page. Manuscripts produced with a dot-matrix printer are ordinarily not acceptable.

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Three sets of clear, unmounted black and white glossy prints of figures should be submitted (preferably 5 by 7 inches, but no larger than 8½ by 11 inches). For line drawings, original artwork or glossy prints are acceptable. Illustrations should be numbered consecutively in Arabic numerals and the position indicated in the text. Figure number, first author's name and top of the photo should be shown on the reverse side of each illustration. Recognizable photographs of patients are to be masked and written permission for publication obtained from the patients.

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References should be limited to those cited in the text and should be to medical, scientific, or scholarly publications. (Mass circulation periodicals are referenced in parentheses in the text.) They must be typed double-space and numbered consecutively as they appear in the manuscript. (See examples below for style.) Abbreviations of journal titles should conform to those used in *Index Medicus*.

Journal Articles

Note handling of multiple authorship. If more than three authors are listed as contributors, use "et al" to designate those names after the first three. Also note capitalization, punctuation, use of inclusive page numbers, and year of publication. Separate the subtitle from the title by either a dash or a colon. Use colon *only* if it appears in the original citation.

1. Jones JS, Anderson HW, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978; 292:444-456
2. Graybill JR, Alford RH, Smith RG, et al: Cell-mediated immunity in cryptococcosis: A brief review. Cell Immunol 1978; 7:76-79

Books

Note handling of "edition," "editor(s)," and "volume," as well as appropriate sequence of reference information and capitalization of chapters and titles.

3. Berne EJ, Smith TL: Role playing in therapy, chap 2, Principles of Group Therapy. New York, Oxford University Press, 1966, pp 35-51 *(author of chapter same as author of book)*
4. Munsung JM: The role of drugs, chap 2, *In* Brest AN, Mayer JH (Eds): Hypertension—Vol 2, Therapy, 2nd Ed. Springfield, Ill, Charles C Thomas, 1961, pp 456-479 *(author of chapter different from authors of book)*

Pamphlets, Monographs, or Books With No Given Author

5. AMA Department of Drugs: AMA Drug Evaluation, 3rd Ed. Littleton, Mass, Publishing Sciences Group, 1977 *(corporate author)*
6. Compilation of Standard Definitions, 3rd Ed. Philadelphia, American Society for Testing and Materials, 1976 *(no given author; give name and place of publisher)*

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Any article accepted for publication should include the name of the journal (appropriately abbreviated) in which it will appear and the phrase "in press" or "accepted for publication" in place of the date of publication.

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Acknowledgments

It is the policy of *WJM* not to print acknowledgments, the feeling being that if a person has contributed enough to a paper to be mentioned, he or she should be included among the authors, or the contribution should be mentioned in the body of the paper or in a footnote.

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Brief manuscripts commenting on articles that have appeared in the journal, containing information of interest to physicians, or discussing issues of the day will be considered for publication. Very short reports of cases, clinical experience, clinical studies, adverse effects, and the like also will be considered. Items for the Correspondence section should not exceed 600 words and should have no more than five bibliographic references and one figure or table.

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References

1. USP DI Update, September/October 1988, p 120.
2. Br J Clin Pharmacol 1985;20:710-713.
3. Data on file, Lilly Research Laboratories.
4. Scand J Gastroenterol 1987;22(suppl 136):61-70.
5. Am J Gastroenterol 1989;84:769-774.

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Carcinogenesis, Mutagenesis, Impairment of Fertility—A two-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose-related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a two-year study in mice, there was no evidence of a carcinogenic effect in male mice, although hyperplastic nodules of the liver were increased in the high-dose males as compared with placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups. The rate of hepatic carcinoma in the high-dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement as compared with concurrent controls and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery are not considered evidence of a carcinogenic potential for Axid.

Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, mouse lymphoma assay, chromosome aberration tests, and a micronucleus test.

In a two-generation, perinatal and postnatal fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

Pregnancy—Teratogenic Effects—Pregnancy Category C—Oral reproduction studies in rats at doses up to 300 times the human dose and in Dutch Belted rabbits at doses up to 55 times the human dose revealed no evidence of impaired fertility or teratogenic effect; but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights. On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in one fetus, and at 50 mg/kg, it produced ventricular anomaly, distended abdomen, spina bifida, hydrocephaly, and enlarged heart in one fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers—Studies in lactating women have shown that 0.1% of an oral dose is secreted in human milk in proportion to plasma concentrations. Because of growth depression in pups reared by treated lactating rats, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

Pediatric Use—Safety and effectiveness in children have not been established.

Use in Elderly Patients—Healing rates in elderly patients were similar to those in younger age groups as were the rates of adverse events and laboratory test abnormalities. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

Adverse Reactions: Clinical trials of varying durations included almost 5,000 patients. Among the more common adverse events in domestic placebo-controlled trials of over 1,900 nizatidine patients and over 1,300 on placebo, sweating (1% vs 0.2%), urticaria (0.5% vs <0.01%), and somnolence (2.4% vs 1.3%) were significantly more common with nizatidine. It was not possible to determine whether a variety of less common events was due to the drug.

Hepatic—Hepatocellular injury (elevated liver enzyme tests or alkaline phosphatase) possibly or probably related to nizatidine occurred in some patients. In some cases, there was marked elevation (>500 IU/L) in SGOT or SGPT and, in a single instance, SGPT was >2,000 IU/L. The incidence of elevated liver enzymes overall and elevations of up to three times the upper limit of normal, however, did not significantly differ from that in placebo patients. Hepatitis and jaundice have been reported. All abnormalities were reversible after discontinuation of Axid.

Cardiovascular—In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in two individuals administered Axid and in three untreated subjects.

CNS—Rare cases of reversible mental confusion have been reported.

Endocrine—Clinical pharmacology studies and controlled clinical trials showed no evidence of antiandrogenic activity due to nizatidine. Impotence and decreased libido were reported with equal frequency by patients on nizatidine and those on placebo. Gynecomastia has been reported rarely.

Hematologic—Fatal thrombocytopenia was reported in a patient treated with nizatidine and another H_2-receptor antagonist. This patient had previously experienced thrombocytopenia while taking other drugs. Rare cases of thrombocytopenic purpura have been reported.

Integumental—Sweating and urticaria were reported significantly more frequently in nizatidine- than in placebo-treated patients. Rash and exfoliative dermatitis were also reported.

Hypersensitivity—As with other H_2-receptor antagonists, rare cases of anaphylaxis following nizatidine administration have been reported. Because cross-sensitivity among this class has been observed, H_2-receptor antagonists should not be administered to those with a history of hypersensitivity to these agents. Rare episodes of hypersensitivity reactions (eg, bronchospasm, faryngeal edema, rash, and eosinophilia) have been reported.

Other—Hyperuricemia unassociated with gout or nephrolithiasis was reported. Eosinophilia, fever, and nausea related to nizatidine have been reported.

Overdosage: Overdoses of Axid have been reported rarely. If overdosage occurs, activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. Renal dialysis for four to six hours increased plasma clearance by approximately 84%.

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(Continued from Page 262)

November 2-3—**Starting Your Practice.** La Posada Hotel, Albuquerque. Fri-Sat. Contact: S. Hill, American Medical Association, 535 North Dearborn St, Chicago, IL 60610. (312) 645-4958.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

September 26—**A Day in Infectious Diseases** (Sponsor: UUMC). Wed. University of Utah, Department of Internal Medicine, Salt Lake City. Contact: (801) 581-8664.

September 27-29—**Pediatric Update** (Sponsor: UUMC). Thurs-Sat. Sun Valley, Idaho. Contact: (801) 581-8664.

October 4-5—**Ethics and Health** (Sponsor: UUMC). Thurs-Sat. University of Utah Alumni House, Salt Lake City. Contact: (801) 581-8664.

October 11-12—**Proper Prescribing of Controlled Substances** (Sponsor: UMA and UUMC). Thurs-Fri. University Park Hotel, Salt Lake City. Contact: UMA.

October 19—**Ophthalmology Clinical Faculty Day** (Sponsor: UUMC). Fri. University of Utah, Department of Ophthalmology, Salt Lake City. Contact: (801) 581-6384.

October 19-20—**Laser Surgery—Laparoscopic Cholecystectomy** (Sponsor: UUMC). Fri-Sat. The Laser Institute, University of Utah, Salt Lake City. Contact: J. Freedman, (801) 581-7001.

October 25-26—**Laser Surgery—Gastroenterology** (Sponsor: UUMC). Thurs-Fri. The Laser Institute, University of Utah, Salt Lake City. Contact: J. Freedman, (801) 581-3293.

November 1-2—**Laser Surgery—General Surgery** (Sponsor: UUMC). Thurs-Fri. The Laser Institute, University of Utah, Salt Lake City. Contact: J. Freedman, (801) 581-3293.

November 9-11—**Laser Surgery—Laparoscopic Cholecystectomy** (Sponsor: UUMC). Fri-Sun. The Laser Institute, University of Utah, Salt Lake City. Contact: J. Freedman, (801) 581-7001.

November 16-17—**Pediatric Update** (Sponsor: UUMC). Fri-Sat. Holiday Inn, St George. Contact: (801) 581-8664.

December 7-9—**Laser Surgery—Laparoscopic Cholecystectomy** (Sponsor: UUMC). Fri-Sun. The Laser Institute, University of Utah, Salt Lake City. Contact: J. Freedman, (801) 581-7001.

January 1-6—**Arthritic Hip, Knee & Shoulder** (Sponsor: UUMC). Mon-Fri. Snowbird. Contact: (801) 581-8664.

January 15-19—**Arthroscopic Surgery 1991** (Sponsor: UUMC). Tues-Sat. Phoenix, Arizona. Contact: (801) 581-7602.

January 17-21—**Ethics and Health** (Sponsor: UUMC). Thurs-Mon. University of Utah, Olpin Union Building, Salt Lake City. Contact: (801) 581-8664.

January 25-27—**Laser Surgery—Laparoscopic Cholecystectomy** (Sponsor: UUMC). Fri-Sun. The Laser Institute, University of Utah, Salt Lake City. Contact: J. Freedman, (801) 581-7001.

February 1-3—**Pediatric Update** (Sponsor: UUMC). Fri-Sun. Jackson, Wyoming. Contact: (801) 581-7001.

February 4-8—**Surgical Pathology** (Sponsor: UUMC). Mon-Fri. Park City. Contact: K. Rassmussen, (801) 379-7178.

February 10-15—**Interventional Radiology** (Sponsor: UUMC). Sun-Fri. Park City. Contact: Judy Gallegos, (801) 581-8188.

February 10-15—**Update in Clinical Microbiology and Immunology** (Sponsor: UUMC). Sun-Fri. Park City. Contact: Midge Beckman, (801) 581-7480.

February 11-16—**Microsurgery Workshop** (Sponsor: UUMC). Mon-Sat. University Park Hotel, Salt Lake City. Contact: (801) 581-8664.

February 11-16—**Orbital & Craniofacial Surgery** (Sponsor: UUMC). Mon-Sat. Snowbird. Contact: (801) 581-8664.

February 11-17—**Family Practice Refresher Course** (Sponsor: UUMC). Mon-Sun. Salt Lake Hilton, Salt Lake City. Contact: K. Chisholm, (801) 581-7234.

February 15-19—**The 35th Anesthesiology Update** (Sponsor: UUMC). Fri-Tues. Snowbird. Contact: V. Larsen, (801) 581-6393.

February 17-20—**The 32nd Annual Ob/Gyn Update** (Sponsor: UUMC). Sun-Wed. The Yarrow, Park City. Contact: S. Martin, (801) 581-5501.

February 19-23—**Pediatric Emergency Medicine** (Sponsor: UUMC). Wed-Sun. The Marriott Hotel, Salt Lake City. Contact: (801) 588-2000.

SPONSORS OF COURSES—ABBREVIATIONS

AHA: American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.

BYUHS: Brigham Young University Health Services, McDonald Student Health Center, Brigham Young University, Provo 84602. (801) 378-2771.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 S 300 East, Salt Lake City 84101. (801) 262-3461.

DMC: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 673-9681.

HCH: Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

144: 144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave, Salt Lake City 84103. (801) 363-1221.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

SMH: St Mark's Hospital, 1200 E 3900 South, Salt Lake City 84117. (801) 268-7111.

UMA: Utah Medical Association, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUMC: University of Utah Medical Center, 50 N Medical Dr, Salt Lake City 84132. (801) 581-2258.

UVRMC: Utah Valley Regional Medical Center, 1034 N Fifth West, Provo 84604. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

VVMC: Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.

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WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

September 20—**Orthopedics.** Everett. Thurs. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

September 20-21—**Critical Care '90.** Tacoma. Thurs-Fri. Contact: Multicare, (206) 594-1221.

September 26—**Rheumatology.** Seattle. Wed. Contact: Northwest Hospital, (206) 368-1622.

October 11—**Diabetes.** Everett. Thurs. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

October 12—**Attorneys and Medicine.** Seattle. Fri. Contact: U/W.

October 16-19—**Indoor Radon and Lung Cancer: Reality or Myth.** Richland. Tues-Fri. Life Sciences Center, Battelle, Pac NW Lab. (509) 376-3665.

October 19—**24th Annual Cancer Conference: Gastrointestinal Cancer in the '90s.** Seattle. Fri. Contact: VMMC.

October 20—**Practice Update for Rural Physicians.** Seattle. Sat. Contact: VMMC.

October 24—**Sexual Dysfunction.** Seattle. Wed. Contact: Northwest Hospital, (206) 368-1622.

November 2—**Diabetes, 1990.** Seattle. Fri. Contact: VMMC.

November 8—**Pediatrics.** Everett. Thurs. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

November 9—**Medical and Surgical Update for Psychiatrists.** Seattle. Fri. Contact: VMMC.

November 14—**Psychiatry.** Seattle. Wed. Contact: Northwest Hospital, (206) 368-1622.

November 15-16—**Drug Therapy.** Seattle. Thurs-Fri. Contact: U/W.

December 7—**Practical Pediatrics.** Seattle. Fri. Contact: VMMC.

December 8—**Gastrointestinal Conference.** Seattle. Sat. Contact: Northwest Hospital, (206) 368-1622.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898. ◆

CURRENT AND FUTURE TRENDS IN CALIFORNIA AMBULATORY HEALTH CARE

October 20, 1990
Westin Hotel, San Francisco Airport

The California Medical Association, in conjunction with the Association of Freestanding Radiation Oncology Centers, the American Society of Outpatient Surgeons, and the Outpatient Ophthalmic Surgery Society, will present a one day educational program on the ambulatory health care accreditation process and issues important to the industry, including:

- Quality Assurance/Risk Management
- Utilization Review
- Reimbursement
- Fraud and Abuse
- Legislative Update
- Subacute Care

Please contact the California Medical Association Ambulatory Care Survey Programs at 415-882-5174 for a brochure and application.

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FAMILY PRACTICE OPPORTUNITY. Association available in rural town, one hour from Seattle and one-half hour from Tacoma. Obstetrics optional. Growing community close to mountains and Puget Sound. Owner to retire in four to five years. (206) 829-1444.

OB/GYN. BC/BE to join 20 physician (OB, Pediatrics, Internal Medicine) practice in sunny central Washington. Reasonable call schedule with three OB/GYN department. Competitive salary, excellent benefit package including vacation at 30 days per year and professional liability. Contact Ann Garza, Yakima Valley Farm Workers Clinic, PO Box 190, Toppenish, WA 98948; (509) 865-5898.

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San Francisco, CA 94120-7602
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OB/GYN, INTERNISTS, Family Practitioners, Pediatricians for Arizona and western opportunities. Quality positions available other regions of country. Inquiries confidential. Mitchell & Associates, PO Box 1804, Scottsdale, AZ 85252; (602) 990-8080.

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RADIOLOGIST. Part-time position available immediately in small hospital with general radiography and fluoroscopy, mammography, and ultrasound in Weaverville, California. Contact Drs Wheeler, Biggs, or Babbitt, West Coast Radiology, 3798 Janes Rd, Ste 12, Arcata, CA 95521; office number (707) 822-3621, ext 191.

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Physician Recruitment
San Luis Medical Clinic
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San Luis Obispo, CA 93401

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- Join the largest department within this multispecialty group (15 Family Practitioners)
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CONTACT:
Colleen Mooney
Recruitment Coordinator
Rockwood Clinic
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Spokane, WA 99202
(509) 838-2531

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ARIZONA. Thomas-Davis Medical Centers, PC, a rapidly expanding multispecialty group practice of 110 plus physicians in Tucson, Green Valley, and Tempe, Arizona, has positions available in these cities in Internal Medicine, Pediatrics, OB/GYN, Orthopedics, and Family Practice. Excellent fringe benefits and profit sharing program. Fee-for-service, as well as owned HMO. Must be BE/BC. Call or write James J. Vitali, CEO, Thomas-Davis Medical Centers, PC, PO Box 12650, Tucson, AZ 85732; (602) 322-8300 or Bill DeLong at (602) 322-2500.

WASHINGTON STATE. 31 physician, multispecialty group is recruiting a BC/BE Family Physician for a 40-hour per week position in our clinic-based Immediate Care Center. Attractive salary and benefit package. No evening call or hospital commitment. Attractive farming and college community of 35,000 in southeastern Washington State. Inquiries and CV to Robert G. Caudill, MD, Walla Walla Clinic, 55 W. Tietan, Walla Walla, WA 99362; (509) 525-3720, ext 285.

(Continued on Page 340)

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AIR FORCE

(Continued from Page 338)

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OB/GYN, PEDIATRICS—Nevada and Washington. Private practices available with established OB/GYN physicians in Seattle suburb, Las Vegas and Sparks/Reno. Hospital sponsored Pediatric practices available in the above locations. For details, call Eloise Gusman, 1 (800) 535-7698 or send CV to PO Box 1685, Covington, LA 70434-1685.

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BC/BE PEDIATRICIAN WANTED for semi-rural community 25 miles south of San Francisco to associate with five member Family Practice group. Send inquiry with CV to Lawrence Bruguera, MD, Coastside Medical Clinic, 225 S. Cabrillo Hwy, Ste 100-A, Half Moon Bay, CA 94019; (415) 726-0211.

(Continued on Page 341)

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Interested applicants should send curriculum vitae and three references to:

Dr Donal A. Walsh
Associate Dean for Curricular Affairs
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University of California, Davis, CA 95616
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Closing date: October 5, 1990

(Continued from Page 340)

ONCOLOGY—Seattle, Washington suburb. Join established Oncologists in private practice. For details, call Eloise Gusman, 1 (800) 535-7698 or send CV to PO Box 1685, Covington, LA 70434-1685.

INTERNISTS—Nevada, California, Texas, Louisiana, Florida! Private practices available to join established physicians or to buy established practices. For details, call Eloise Gusman, 1 (800) 535-7698 or send CV to PO Box 1685, Covington, LA 70434-1685.

COASTSIDE MEDICAL CLINIC. BC/BE Family Practitioner wanted for semi-rural community only 25 miles south of San Francisco with five member Family Practic group. Send inquiry and CV to Lawrence Bruguera, MD, 225 S. Cabrillo Hwy, Ste 100-A, Half Moon Bay, CA 94019; (415) 726-0211.

ALBUQUERQUE, NEW MEXICO. BC/BE Family Practitioners sought to join established, private practice, single specialty group practice. Income guarantee, benefits. Please send CV to Kathryn Rhoades, Presbyterian Healthcare Services, PO Box 26666, Albuquerque, NM 87125-6666, or call 1 (800) 545-4030, ext 6330.

ORTHOPEDIC SURGEONS, BC/BE sought for expanding group in Sacramento. Currently seeking experienced hand/upper extremity, spine, and general Orthopedists. Excellent growth and compensation potential. Limited call schedule, flexible hours, med/legal evaluations. Send CV to Number 214, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

INTERNIST—PACIFIC NORTHWEST. Excellent opportunity for BC/BE Internist to join group of five Internists in suburban Idaho community. Near urban referral center with good subspecialty backup. Also near superb hunting, fishing, camping, and skiing. Please call or refer résumé to Susan Davis, Administrator, Caldwell Internal Medicine Professional Association, 222 E. Elm, Caldwell, ID 83605; 1 (208) 459-4667.

SALT LAKE CITY. Family Practice and Urgent Care. Excellent opportunity in southeast suburb. Patients from upper middle class. Practice is busy and growing rapidly. Excellent salary with partnership in one year. Send CV to Mark Anderson, MD, 580 E. 9400 South, Salt Lake City, Utah 84070; (801) 975-1600.

OB/GYN—BC/BE. Position with a multispecialty 54 physician group practice. Join five BC OB/GYN physicians in a practice with an established growth pattern in community of 120,000 plus. Marysville Medical Group was founded in 1938 and is the largest private practice group in rural northern California, owned and governed by its own physicians. Send CV to Warren J. Boyer, MD, Medical Director, Marysville Medical Group, 800 Third St, Marysville, CA 95901.

DENVER: Primary Care Physician for ger/adults and one BE/BC Psychiatrist $74,294 plus benefits, faculty appointment. Contact B. J. Brooks, MD, Assoc Director, FLMHC, 3520 W. Oxford Ave, Denver, CO 80236; (303) 762-4117. AA/EOE.

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SEATTLE: BC/BE General Internist to practice on Mercer Island, join BC Internists' group with three Seattle area offices. No income guarantee; group and location excellent. Write Dr Paxson, 3236 78th Ave SE, Ste 104, Mercer Island, WA 98040.

FAMILY PRACTITIONER needed for growing country community, unlimited potential, acute hospital 10 miles, one hour freeway drive to Sacramento, suite available in Medical/Dental building. For more information write or call Colusa County Economic Development Corporation, Box 1101, Williams, CA 95987; (916) 473-5383, or Williams Civic Association, Box 908, Williams, CA 95987.

CENTRAL OREGON. Family Practitioner sought for 7 member Family Practice group in heart of Oregon's best outdoor recreation. BE/BC Family Practitioner with experience in OB preferred. Excellent opportunity close to Cascade Mountains—skiing, hiking, fishing. Contact Jean Erickson, PROSEARCH, 305 NE 102nd Ave, Portland, OR 97220; (800) 622-3377.

FAMILY PRACTICE RESIDENCY DIRECTOR and full-time faculty position for BC Family Physician in an 18 resident, eight faculty program affiliated with University of California, Davis. Large clinical component with inpatient, outpatient, and routine OB skills needed. Send inquiries to T. N. Ernst, MD, PO Box 231, Merced, CA 95340-0231; (209) 385-7172.

(Continued on Page 342)

(Continued from Page 341)

PHYSICIANS WANTED

PALO ALTO MEDICAL CLINIC
PALO ALTO, CALIFORNIA

A well-established, 150-physician multi-specialty group with a national reputation for innovation and excellence is seeking BE/BC physicians in the following specialties for its main campus and satellite:

GENERAL INTERNAL MEDICINE
PSYCHIATRY
OCCUPATIONAL MEDICINE
OBSTETRICS/GYNECOLOGY
PHYSIATRY
FAMILY PRACTICE
URGENT CARE
NUCLEAR MEDICINE
HEMATOLOGY/ONCOLOGY

Salaries and benefits are competitive, partnership eligibility in two years, San Francisco Bay Area living.

Please contact: George Perlstein, M.D.
Medical Director
Palo Alto Medical Clinic
300 Homer Avenue, Palo Alto, CA 94301
(415) 853-4762

PHYSICIANS WANTED

Western States OPENINGS

Many multispecialty groups and hospitals have asked us to recruit for over 300 positions of various specialties. Both permanent and locum tenens. Send CV to:
Western States Physician Services
5414 E. Montecito, Fresno, CA 93727
Or call 1 (800) 873-0786

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Director
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1-800-527-2145

EGSI, 1717 Main Street, Suite 5200
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DERMATOLOGY
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PEDIATRICS
FAMILY PRACTICE
GASTROENTEROLOGY
OCCUPATIONAL MEDICINE
HEMATOLOGY/ONCOLOGY
NEPHROLOGY
RHEUMATOLOGY
GENERAL SURGERY
ORTHOPEDICS

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CONTACT: **Colleen Mooney, Recruitment Coordinator**
Rockwood Clinic, PS
E. 400 Fifth Ave
Spokane, WA 99202
(509) 838-2531

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(Continued on Page 344)

SPECIAL ISSUES

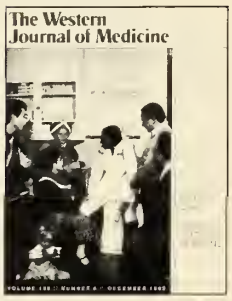
Addiction Medicine
and the Primary Care Physician

Addiction Medicine and the Primary Care Physician was conceived to be part of the initiative to expand the involvement of all specialties of medicine in the prevention and treatment of addictive disease. Topics covered include chemical dependence and the workplace, alcoholism, methadone maintenance in the treatment of opioid dependence, nicotine dependence, and treatment of cocaine dependence. David Smith MD, Special Editor, 1990.

Women and Medicine

This special issue explores both the professional side of women in medicine and the diagnosis and treatment of women patients. Topics covered include liver disease, women and AIDS, heart disease, hysterectomy, PMS, ovarian cancer, and women physicians and organized medicine. Linda Hawes Clever, MD, Special Issue Editor, 1988.

Cross-cultural Medicine



Cross-cultural medicine is devoted to the care of patients of different cultural, ethnic, or religious backgrounds. Subjects include Southeast Asian refugees in the American health care system, psychiatry and Chinese culture, health and illness in Filipino immigrants, and health care of Middle Eastern patients. M. Margaret Clark, PhD, Special Issue Editor, 1983. 2nd reprinted edition.

Also available:

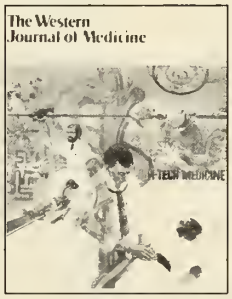
AIDS—A Global Perspective

Jonathan M. Mann, MD
Special Issue Editor, 1987

Medical Informatics

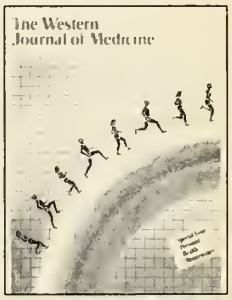
Marsden S. Blois, MD
Special Issue Editor, 1986

High-Tech Medicine



R. Paul Robertson, MD
Special Issue Editor, 1985

Personal Health Maintenance



John H. Holbrook, MD
Special Issue Editor, 1984

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P.O. Box 7602, San Francisco, CA 94120-7602

(Continued from Page 342)

PHYSICIANS WANTED

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If interested, call me at (702) 877-8638 or send your CV to:

Jerry Reeves, MD, President, Southwest Medical Associates
PO Box 15645, Las Vegas, NV 89114

UNIVERSITY OF CALIFORNIA, DAVIS MEDICAL CENTER. The University of California, Davis, Department of Emergency Medicine is searching for physicians residency trained or BC in Emergency Medicine. The Health Science Campus is located in Sacramento and serves a large area of northern California. The Emergency Department cares for over 60,000 patients a year. The Center operates as a Level One Trauma Center, has paramedic base station training responsibilities, and has a helicopter service. An approved Emergency Medicine Residency Program began in July 1990. Emergency Physicians supervise medical students, interns, and residents, in addition to having direct patient responsibilities. Support for clinical research is available to those interested. University compensation is competitive, and fringe benefits include health and dental insurance, three weeks paid vacation, one week continuing medical education, social security, UC retirement plan, 12 paid holidays per year, and full malpractice coverage. Send CV to Robert W. Derlet, MD, Chief, Division of Emergency Medicine, University of California, Davis, Medical Center, 2315 Stockton Blvd, Sacramento, CA 95817.

ALASKA—The only Vitro-Retinal specialist in Anchorage is now seeking an associate with similar skills. For more information send CV to Gordon Crawford, Manager, Professional Relations, Humana Inc, Dept HH-9B, 500 W. Main St, Louisville, KY 40201-1438, or call toll-free 1 (800) 626-1590.

ALASKA—A 10 physician multispecialty group in Anchorage is now seeking to add their second Neurologist. For more information send CV to Gordon Crawford, Manager, Professional Relations, Dept HH-9A, 500 W. Main St, Louisville, KY 40201-1438, or call toll-free 1 (800) 626-1590.

SOUTHERN CALIFORNIA (San Diego County). Thriving coastal city of Encinitas. Three Physician Family Practice Group plus Psychologist seeking residency trained Family Practitioner. Located in new Primary Care/Multispecialty full service facility eight minutes from hospital. Send CV to NCFMG 477 El Camino Real, A306, Encinitas, CA 92024.

OREGON. General Internal Medicine, BC/BE, sought for 10 member, multispecialty group in beautiful rural community, population 16,500, 38 miles southwest of Portland. Send CV to Administrator, 420 E. Fifth St, McMinnville, OR 97128; (503) 472-6161.

INFECTIOUS DISEASE PHYSICIAN, BE/BC, to join busy Internal Medicine/Cardiology practice one hour from Los Angeles. Excellent benefits. Send CV to Number 218, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

CARDIOLOGIST—INVASIVE/NONINVASIVE BE/BC, to join four member busy Cardiology practice in small town, one hour from Los Angeles. Full range of noninvasive Cardiology and active Cath Lab. Position available immediately. Send CV to Number 218, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

CALIFORNIA, NORTHERN. A stable group of four ABEM certified/eligible MDs at coastal hospital of 24,000 patient visits would like two new associates. Income $60-$75 per hour. Will consider Family Practice but prefer Emergency Department trained Emergency Physician. Coastal paradise near redwood national parks, minutes from Klammath, Rogue, and Smith Rivers. Video tape of area available. Send CV to EPMG, 120 Montgomery St, Ste 1000, San Francisco, CA 94104.

ASSOCIATED EMERGENCY PHYSICIANS, INC.
Medical Group of Northern California
1625 The Alameda, Suite 201
San Jose, CA 95126

Experienced Emergency Physicians with ACLS/ATLS certification needed to staff moderate volume Emergency Department located in San Francisco.

- Excellent opportunity for highly-skilled, personable physicians interested in teaching house staff and providing quality Emergency Care.
- Established Emergency Physician group with 13 years experience.
- Excellent compensation. Malpractice paid.

Please contact: Nanette Peter, Recruitment Coordinator
(408) 293-8881

PHYSICIANS WANTED

PHYSICIANS NEEDED

The continuing growth of our service area population (now 90,000) has created an immediate need for additional BC/BE physicians in the following specialities:

- **NEUROLOGY.** Establish private practice with no investment, guaranteed income. Proficiency in EEG, EMG required.
- **GENERAL/THORACIC SURGERY.** Establish private practice in General and Thoracic Surgery (no open heart) with no investment, guaranteed income.
- **ONCOLOGY.** Establish private practice with no investment, guaranteed income. Some General Internal Medicine necessary initially.
- **ORTHOPEDIC SURGERY.** No investment, guaranteed income. Above average earning potential.
- **EMERGENCY MEDICINE.** Hospital position. BC/8E in Emergency Medicine, or equivalent combination of appropriate residency training and Emergency Medicine experience. California license required. Competitive remuneration, paid malpractice insurance, individual contract, flexible scheduling. CE allowance. Part-time for double coverage also available.
- **RADIOLOGY.** Hospital group position. Excellent salary and benefit package. Competency in ultrasound, CAT, Nuclear Medicine, film screen mammography, and general diagnosis required. MRI experience desired. Inpatient and outpatient. (California license is required.)

112-bed full service hospital, very well equipped. Excellent ancillary services. Our service area population is now 90,000; a growing area with new businesses and a stable economy.

Located in central California near Sequoia National Park, Tulare offers an excellent family oriented lifestyle and all expected amenities. Beautiful homes, close to hospital and office, are affordably priced. Good schools, many community activities, and abundant recreation including golf, tennis, skiing, mountain and equestrian activities. Easy access to all California's major metropolitan and resort areas.

Contact:
Tulare District Hospital
Physician Recruiting Office
PO Box 90112
Los Angeles, CA 90009
(800) 468-2687

GASTROENTEROLOGIST. Position for a BC/8E gastroenterologist with a multispecialty 54 physician group practice. Certified endoscopy unit and complete in-house radiology and nuclear medicine. Join a practice with an established growth pattern in community of 120,000 plus. Marysville Medical Group was founded in 1938 and is the largest private practice group in rural northern California owned and governed by its own physicians. Send CV to Warren J. Boyer, MD, Medical Director, Marysville Medical Group, 800 Third St, Marysville, CA 95901.

EXCELLENT OPPORTUNITY for energetic, personable Internist, 8C/BE, to assume established practice in eight physician Internal Medicine group in family oriented residential community on San Francisco Bay. Convenient to community hospital; opportunity for teaching appointment. Practice includes EKG reading and once weekly night call plus rapid advancement to full partnership and above average remuneration. Contact Barbara Schneider, Manager, Alameda Medical Group, 501 South Shore Center W, Alameda, CA 94501; (415) 521-2025.

A GROWING RURAL COMMUNITY of 40,000 has openings for two General Surgeons to join a busy practice. Located in eastern New Mexico, Clovis boasts a 100-bed hospital. Salary first year; potential partnership in practice with a Urologist, a Vascular Surgeon, and two General Surgeons. If interested, please send your CV to Bill Norris, Southwest Community Health Services, Physician Recruitment, PO Box 26666, Albuquerque, NM 87125.

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PHYSICIANS WANTED

As one of the nation's oldest and largest managed health care companies, CIGNA Healthplan understands the environment and resources physicians need to practice quality medicine. Currently we have the following opportunities available:

PHYSICIAN ADMINISTRATOR

You will maintain an active clinical practice with a proportion of time dedicated to leadership and management of physician and support staff. Qualifications must include Board Certification in a clinical specialty and prior management experience.

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Part-time, flexible schedules as well as full-time positions are available in Los Angeles and Orange counties.

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A variety of opportunities are available at our 30 health care centers throughout southern California.

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Professional Recruitment Dept.
CIGNA Healthplans of CA
505 N. Brand Blvd, Ste 400-49
Glendale, CA 91203

FAMILY PRACTICE FACULTY—LOS ANGELES. Associate director/clinic director for Family Practice residency program. Rewarding position with competitive salary and benefits. Excellent facilities/stimulating colleagues. Experience desired. Glendale Adventist Med Ctr, call Dr Mary Ferris (818) 500-5594.

23 PHYSICIAN GROUP PRACTICE. Recent population growth and demand have created the need for several specialists including OB/GYN, Cardiology, and Pediatrics in this 23 physician group practice. Situated 60 miles east of San Francisco, the group serves a local population of 35,000. Nearby skiing and boating, reasonable housing, and an excellent school system. Please contact Mary Letterii, Vice President, Physicians Search Group, 120 Montgomery St, Ste 710, San Francisco, CA 94104; (415) 399-8840.

OCCUPATIONAL MEDICINE, SAN FRANCISCO BAY AREA. Area's leading multispecialty private group practice is seeking BC/BE physician to join their expanding Department of Occupational Medicine. Range of practice includes pre-employment physicals, diagnostic evaluations, treatment of on-the-job injuries; comprehensive knowledge of all areas of Occupational Medicine. Competitive salary, plus incentive, excellent benefits, paid malpractice. Located in the South Bay which offers wonderful cultural/recreational activities, fine dining, outstanding climate and scenery, easy access to beach and mountains. For further information, please send CV or contact Maureen Forrester, San Jose Medical Group, Inc, 45 S. 17th St, San Jose, CA 95112.

OCCUPATIONAL PHYSICIAN. Major multispecialty group with large Occupational Medicine department is seeking a clinically oriented, BC/BE Occupational Medicine Physician or physician with other Board Certification and experience in Occupational Medicine. Please contact Dr Kim Fuller, Director, Occupational Medicine Dept, Sharp Rees-Stealy Medical Group, Inc, 2001 Fourth Ave, San Diego, CA 92101, or call (619) 699-1524.

PHYSICIANS WANTED

CALIFORNIA

Primary Care Physicians and Radiologists needed to work as *locum tenens* statewide. High salary, paid malpractice. Work whenever and wherever you wish. Permanent placements as well. **Western Physicians Registry: Northern California, contact Jim Ellis, Director, (415) 673-7676 or (800) 437-7676. Southern California, contact Tracy Zweig, Director, (805) 643-9346 or (800) 635-3175.**

OB/GYN (Flexible Hours) BAY AREA

Opening for general OB/GYN BC/BE to provide coverage and regular OB for high risk group based at prestigious hospital. Gynecology experience can be arranged if desired. Excellent support services. 40 hours per week with flexible/concentrated scheduling. Could be suitable for commuters from other parts of California. Call:

Anders Karlman, Karlman Associates
1 (800) 634-3561

PULMONOLOGIST—University of Nevada School of Medicine. Assistant to full professor depending on qualifications. BC/BE in Pulmonology and eligible for licensure in Nevada. Appropriate administrative, academic teaching and clinical experience, research experience desirable. Supervision of residents, teaching of students, and direct patient care. Submit letter of application, CV and names of three references to Stanley Shane, MD, Internal Medicine, University of Nevada School of Medicine, Reno, NV 89557. Search will continue until position filled. AA/EOE.

STAFF PHYSICIAN. Join us in providing comprehensive medical care for 330 developmentally disabled children and adults at the Wyoming State Training school. Three physicians and one physician's assistant staff our 18-bed health care center and provide medical support to nursing, therapists, professional and paraprofessional staff across campus. Good working relationships with excellent hospital and medical group in local community. Progressive habilitation-oriented working environment. Attractive benefits, malpractice insurance provided, no overhead. Annual salary range $50,000 to $70,000 depending upon experience and qualifications. Campus situated in pleasant west-central Wyoming community of Lander, minutes from beautiful Wind River Mountain Range and close to Yellowstone and Grand Teton National Parks. Outstanding hiking, fishing, hunting, skiing, wilderness areas nearby. Good schools and services, low cost of living, no state income tax. Contact Director of Clinical Services, Wyoming State Training School, 8204 State Highway 789, Lander, WY 82520; or call (307) 332-5302. Equal Opportunity Employer.

COASTAL CALIFORNIA 45,000 population. Well-trained 12 physician primary care group. Immediate/future need for Family Practice and Internal Medicine. Competitive salary and benefits with partnership after one year. On call schedule allows time for family and recreation. In Lompoc, you can do what you were trained to do, including OB, Pediatrics, and General Medicine. Please contact Ken Baker, President, Physician Search Group, 120 Montgomery St, Ste 710, San Francisco, CA 94104; (415) 399-8840.

EMMETT, IDAHO, rural community of 5,000 (12,000 in county) located 25 miles from Boise, is seeking residency trained Family Practitioner to enter full-time practice. First year salary guarantee $60,000 with incentive. Located close to several downhill ski areas as well as many other recreation opportunities such as hunting, fishing, camping. Inquires: please call Newton States, Hospital Administrator, (collect) (208) 365-3561.

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HSI currently has numerous opportunities in California and Washington state for qualified physicians and Orthopedic Surgeons. These positions offer:

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Irvine, CA 92715
(714) 476-9163

OCCUPATIONAL MEDICINE PHYSICIAN. San Francisco Fire Department seeks BC/BE Occupational Medicine Physician to administer comprehensive medical program for 1,500 firefighters. Position responsibilities include medical examinations, developing and implementing primary and secondary prevention strategies, risk management, database accrual and accountability, and management and supervision. Candidates must have suitable background for clinical-faculty appointment to UCSF. Position will include the opportunity for teaching/research with occupational health residents through UCSF. Send résumé to SFFD, 260 Golden Gate Ave, San Francisco, CA 94102, attn: Ray Connors, no later than October 15, 1990. EOE M/F/H/V.

SOUTHERN CALIFORNIA—SPINE SURGEON. An Orthopedic Surgeon with training in Spine Surgery is needed to join two busy, well established Orthopedic Surgeons in Los Angeles County. Unlimited potential since this expertise is not represented in the group's service area. For more information about this opportunity, call toll-free 1 (800) 626-1590, or send your CV to Gordon Crawford, Professional Relations, Humana Inc, Dept HH-9C, 500 W. Main St, Louisville, KY 40201-1438.

NORTHERN CALIFORNIA—SAN FRANCISCO BAY AREA. Leading HMO is seeking BC/BE physician to staff a busy, urban, full-service Emergency Department with the possibility of administrative advancement. Kaiser Permanente is a large pre-paid HMO offering competitive salary, job security, shareholder status, and generous benefits including health care, life insurance, disability insurance, sick leave, mortgage assistance, and educational leave. Please address all inquiries to David Witt, MD, Emergency Department, Kaiser Permanente Medical Center, 1200 El Camino Real, AD-WJM, South San Francisco, CA 94080-3299; or call (415) 742-2516. EOE.

(Continued on Page 346)

(Continued from Page 345)

PHYSICIANS WANTED

RADIOLOGIST—SAN FRANCISCO BAY AREA. Growing outpatient imaging practice with CT/MRI. Salary leading to partnership. Send CV to Murray Solomon, MD, 450 Sutter St, Ste 835, San Francisco, CA 94108; (415) 296-8654.

WYOMING—EMERGENCY MEDICINE. Position available for experienced Emergency Physician (prefer BC/BE in Emergency Medicine) in Rock Springs, Wyoming. Annual ED census 15,000 plus. Excellent occurrence malpractice insurance. Excellent medical and nursing staff. Contact High Desert Emergency Physicians, PC, PO Box 2452, Rock Springs, WY 82902; or T. Michael Mains, MD, at (307) 362-3711.

PEDIATRICIAN BC/BE for hospital-based teaching practice. Interest and training in Neonatology and Critical Care Pediatrics preferred. Join three full-time Pediatricians, two full-time Neonatologists, and one full-time Pediatric Surgeon in hospital with Community Level NICN and busy inpatient and outpatient services. Paid malpractice. Salary negotiable based on training and experience. Submit CV and references to Patricia A. Dixon, MD, Director, Pediatrics/Neonatal Services, San Joaquin General Hospital, PO Box 1020, Stockton, CA 95201; (209) 468-6600. AA/EOE.

ENDOCRINOLOGIST, SANTA FE, NEW MEXICO needed to join flourishing private practice. Contact Robert M. Bernstein, MD, at 1533-B St Francis Dr, Santa Fe, NM 87501.

LAKE ARROWHEAD, CALIFORNIA. Immediate openings for Emergency Physicians to staff low volume emergency department in wonderful location. Directorship also available. Guaranteed $115,000 per year. Directorship $130,000 per year; paid malpractice. Contact Richard Gillespie, MD, Quantum Emergency Medical Associates, PO Box 2467, Santa Rosa, CA 95405; (707) 546-4199.

MONTEREY PENINSULA, CALIFORNIA. BC/BE Primary Care Internist to join multispecialty group in ocean front resort community. Adjacent to Pebble Beach, Carmel. Guaranteed income leading to partnership in eight to twelve months. Busy, well established practice. Excellent office, lab, and x-ray departments. Outstanding community hospital. Submit CV, availability date to John D. Lord, MD, Central Medical Group, 505 Central Ave, Pacific Grove, CA 93950.

SAN FRANCISCO/EAST BAY. Experienced Primary Care Physicians needed at an Emergency Service fast track. This may be a part-time position; our need is for 32 hours per week in eight hour shifts on Saturdays and Sundays only. Physicians may work from one to four weekends a month. Remuneration is hourly and is highly competitive for the bay area. PO Box 5138, Berkeley, CA 94705.

SACRAMENTO—BE/BC General Internists. Successful stable multispecialty group. Opportunity to practice full range of inpatient and outpatient Internal Medicine. Full access to diagnostic, therapeutic, and consultative services. Academic affiliation with University of California, Davis, teaching residents in our hospital. In house CME. We are Kaiser Permanente—a physician managed, well established steadily growing group. Outstanding starting salary and advancement, benefit package, and retirement. Sacramento is California's boom town. Excellent schools. Family life-style. This is a quality career opportunity. Please call or send CV to Dennis Ostrem, MD, The Permanente Medical Group, Inc, 2025 Morse Ave, Sacramento, CA 95825; (916) 973-5781. EOE.

CENTRAL CALIFORNIA. Hospital based teaching opportunity for OB/GYN in a new Residency Program at the KMC. Ideal candidate is a team player with a strong desire to teach residents. This UCLA affiliate has a busy OB department with 5,000 deliveries per year. Please contact Mary Letterii, Vice President, Physicians Search Group, 120 Montgomery St, Ste 710, San Francisco, CA 94104; (415) 399-8840.

PHYSICIANS WANTED

FULL-TIME TRAVEL REQUIRED (one year minimum). Health research organization needs physicians for National Health and Nutrition Examination Survey sponsored by the US Public Health Service. Individuals will be part of a large medical team conducting health examinations in government examination centers traveling to 68 areas of the US through 1993. Physicians must be licensed in one state. Competitive salary, paid malpractice, per diem, car, four weeks paid vacation per year, holidays, and health, life, dental, disability insurance offered. Call Beverly Geline at (800) 937-8281, ext 8248. Westat, Inc, Rockville, MD. EOE/M/F/V/H.

CALIFORNIA, MONTEREY BAY. Full-/part-time positions available with Monterey Bay's largest and most successful Urgent Care network. Generous guarantee, incentive plan, and benefit package. Malpractice covered. Practice in California's most beautiful coastal recreational area. BC/BE Emergency Room Medicine or Family Practice specialists preferred. Contact Bob Morris, MD, FACEP, Doctors on Duty Medical Clinics, 223 Mt Hermon Rd, Scotts Valley, CA 95066; (408) 438-9341.

DOWNEY, LOS ANGELES COUNTY, Family Practitioner or General Internist. Immediate full-time opening for a primary care physician to a new Neurology/Stroke rehabilitation inpatient unit with ambulatory care population. Regular hours without nighttime or weekend call. Rancho Los Amigos Medical is a Los Angeles County hospital and a teaching hospital affiliated with the University of Southern California. Good opportunity for teaching and/or research. California license required. Rancho Los Amigos is an affirmative action equal opportunity employer. Interested individuals should send CV to Milton Fort, MD, Rancho Los Amigos Medical Center, Neuro/Stroke Service, Rm 7, 700 Annex, 7601 E. Imperial Hwy, Downey, CA 90242.

SOUTHERN CALIFORNIA. Young Family Practitioner with dynamic practice seeking associate for future partnership. Generous salary/guarantee and incentives package. New medical office near outstanding 300-bed community hospital. Growing community within one hour of beaches and mountains. Ken Baker, PSG, 120 Montgomery St, Ste 710, San Francisco, CA 94104; (415) 399-8840.

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Kaiser Permanente, Northwest Region, has excellent opportunities available immediately and in 1991 for BC/BE Family Physicians.

Our medical offices are located in the Portland/Vancouver area; Salem, Oregon; and Longview, Washington, providing a full range of professional services to 375,000 Kaiser Permanente members regionwide.

Experience the quality of life in the beautiful Pacific Northwest; close to mountains and beaches. We offer a competitive salary and benefits, senior physician standing after two years, sabbatical, and professional liability coverage. Forward CV and inquiry to:

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Northwest Permanente, PC
3600 N. Interstate Ave
Portland, OR 97227.
EOE.

KAISER PERMANENTE
Northwest Permanente P.C.
Physicians and Surgeons

PHYSICIANS WANTED

PEDIATRICIAN — FACULTY POSITION/NORTHERN CALIFORNIA. Pediatric department of Family Practice residency program affiliated with University of California, Davis, seeks sixth BC/BE Pediatrician for a teaching position. Duties include teaching and patient care on inpatient Pediatric service, busy nursery, and clinics. Neonatal resuscitation skills are necessary. We offer a competitive salary and benefits. Easy access to recreational and cultural opportunities of San Francisco bay area. Send CV and letter of application to Diane Dooley, MD, Chairperson, Dept of Pediatrics, Merrithew Memorial Hospital, 2500 Alhambra Ave, Martinez, CA 94553; (415) 370-5110. EOE.

MARYSVILLE (YUBA CITY). Primary care provider. Northern California primary care clinic with large Medi-Cal clientele. Three physicians, two physician assistants. No OB. No surgery. Near mountains, close to Sacramento, 2½ hours to Lake Tahoe and San Francisco. Salary $86,113 plus. Please contact Ed Allen, 938 14th St, Marysville, CA 95901; or call (916) 741-6244.

INTERNAL MEDICINE, NORTHERN CALIFORNIA. You have a unique opportunity to join the area's leading multispecialty private medical practice. A position is available immediately for a BE/BC Internist. Subspecialties welcome to apply. Generous salary, bonus provision, fringe benefit package, and early membership in the corporation. Accept the challenge; become part of our competitive, growing organization. Experience the good life—wonderful restaurants, beautiful scenery, great weather, cultural facilities, easy access to beaches and mountains. Send CV and receive further information by contacting Maureen Forrester, Physician Recruitment, 45 S. 17th St, San Jose, CA 95112; (408) 282-7833, (408) 282-7757.

BC RADIOLOGIST. Position with a multispecialty 54 physician group practice—no hospital. Expertise in conventional diagnostic radiology, ultrasound, mammography, nuclear medicine, CAT, and uroradiology. Three Radiologists, with a staff of 14, do approximately 55,000 procedures annually. Marysville Medical Group was founded in 1938 and is the largest private practice group in rural northern California owned and governed by its own physicians. Send CV to Warren J. Boyer, MD, Medical Director, Marysville Medical Group, 800 Third St, Marysville, CA 95901.

SAN FRANCISCO BAY AREA—Occupational Health/ambulatory care center, Monday through Friday days; no nights, weekends or holidays required. Seeking Family Practice or Emergency Medicine experienced physician with keen interest in Occupational Medicine. Salary $100K plus. Send CV to Chase Dennis Group, 400 Taylor Blvd, #330, Pleasant Hill, CA 94523; (415) 676-2555.

KAISER PERMANENTE

Good People. Good Medicine.

NORTHERN CALIFORNIA

Several positions available for Family Practice, Internal Medicine, and most medical subspecialties. We are a young, aggressive group in a well known prepaid group practice HMO organization with excellent benefits and a very reasonable call schedule. You will have a rewarding practice opportunity with ample time to enjoy the mountains and San Francisco which are nearby. If interested please call or send CV to Physician Recruitment, Administration, The Permanente Medical Group, Inc, 1305 Tommydon St, Stockton, CA 95210; (209) 476-3300.

(Continued on Page 348)

The Permanente Medical Group, Inc.
Northern California

Quality

Stability

Leadership

Growth

Support

Rewards

The Permanente Medical Group, Inc., the largest multispecialty group practice in the U.S., is undergoing explosive growth in its Northern California region: the San Francisco Bay Area, Sacramento and the Central Valley. Our rapid increase in membership has created practice opportunities throughout the region.

Our physician-managed group is part of the comprehensive Kaiser Permanente Medical Care Program. As a TPMG physician, you have access to the latest medical technology and resources, the support of colleagues in all subspecialties — and the opportunity to provide excellent health care without the burdens of managing a practice.

Join us in one of these facilities:

- Walnut Creek/Pleasanton/Danville
- Martinez/Antioch
- Oakland
- South Sacramento/Stockton
- Santa Rosa
- San Jose/Gilroy
- San Francisco
- South San Francisco
- Sacramento/Roseville/Davis/ Rancho Cordova
- Richmond
- Redwood City
- Fresno
- Hayward/Fremont
- Santa Clara/Milpitas/Sunnyvale
- Vallejo/Fairfield/Napa
- San Rafael/Petaluma/Novato

TPMG offers many benefits: scheduled time off with cross-coverage provided by your colleagues, continuing education, malpractice insurance, a substantial retirement program and special arrangements for physicians transferring from established practice. For complete information, call or send CV to: The Permanente Medical Group, Inc., Richmond Prescott, M.D., Physician Recruitment Services, Dept. WJM-9240, 1814 Franklin, 4th Floor, Oakland, CA 94612. (800) 777-4912. Equal Opportunity Employer.

KAISER PERMANENTE
Good People. Good Medicine.

(Continued from Page 346)

PHYSICIANS WANTED

SAN FRANCISCO BAY AREA BC/BE INTERNISTS

We are currently seeking highly qualified Internists and subspecialists to complement our energetic Internal Medicine team. Department members provide a full range of medical services for a population of over 200,000 pre-paid health plan members. Recently renovated and expanded medical center facilities are within convenient commuting distance to virtually any bay area city, and the extensive cultural and recreational activities of northern California. As part of our large, multispecialty group practice, you would enjoy an excellent salary, generous fringe benefits, a flexible schedule, and the opportunity for academic affiliation with prestigious local institutions. Send CV to:

Winslow Wong, MD
Attn: Administration
Kaiser Permanente Medical Center
27400 Hesperian Blvd
Hayward, CA 94545

EOE

ALL SPECIALTIES/DESIRABLE PRACTICE OPPORTUNITIES AVAILABLE NATIONWIDE

Let us find you the practice that meets your specifications and geographical preference. There is no fee to the physician for our professional service. All inquiries are held in strict confidence. BC/BE physicians send CV or call:

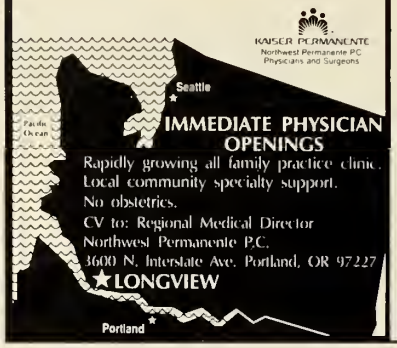
Sharon Mac Kenzie
Mac Kenzie & Associates
PO Box 1240
Trinidad, CA 95570
1 (800) 735-4431
FAX: (707) 677-3033

VICE CHAIRMAN University of Nevada School of Medicine, Department of Family and Community Medicine. Associate/full professor depending on qualifications. Must for ABFP certified and eligible for licensure in Nevada. Previous experience as Family Practice Residency Director or similar administrative/teaching position preferred. Joining new successful program in community based medical school. Responsible for overall administration of Las Vegas section of department. Includes third year medical student clerkship/Family Practice residency. Position includes some direct patient care, including Obstetrics. Send CV to George Hess, MD, Chairman, Dept of Family and Community Medicine, University of Nevada School of Medicine, Reno, NV 89557. Search will continue until position filled. AA/EOE.

FAMILY PRACTICE—SACRAMENTO. Kaiser Permanente is seeking BC/BE Family Practice Physicians to join the Division of Family Practice. We offer a challenging position that provides both outpatient and inpatient experience and enjoys close support from the specialty departments. We offer our patients high quality medicine and our physicians a practice with a high degree of professional and personal satisfactions. You will be joining a unique organization with a long, successful track-record and will benefit from the financial security associated with its success. Sacramento is a large diverse city providing a relative low cost of housing and is rich in cultural activities. It is also 90 miles from San Francisco and Lake Tahoe recreation areas. For additional information contact Stuart Hahn, MD, The Permanente Medical Group, Inc, 3240 Arden Way, Sacramento, CA 95825; or call (916) 973-5546. EOE.

PHYSICIANS WANTED

LONGVIEW, WASHINGTON



Longview is a picturesque, stable community of 42,000 located near the Columbia Gorge and the coastal mountains and beaches of Washington and Oregon. Members of our 12 physician group enjoy individual subpractices, infrequent call, and new state-of-the-art medical offices.

We invite you to contact us at the above address regarding practice opportunities. Or call Judy Parmenter, Physician Recruitment, (503) 280-2050 for further information.

NORTHERN CALIFORNIA. Immediate openings for Emergency, Family Practice, and General Internal Medicine physicians who desire to work in the wine country north of San Francisco. Positions available in moderate volume emergency departments and Ambulatory Care Center. A unique opportunity is also available for Family Practice and Internal Medicine physicians who desire to practice Inpatient Medicine without the hassles of an office practice. Guaranteed $90-$110,000 per year; paid malpractice. Contact Richard Gillespie, MD, Quantum Emergency Medical Associates, PO Box 2467, Santa Rosa, CA 95405; (707) 546-4199.

BC/BE OB/GYN, CALIFORNIA. Position offers excellent salary $150,963 to $175,170 plus comprehensive benefit package in desirable central California location. Multispecialty group practice sponsored by County with all inpatient work done in private hospitals. Located near Sequoia National Park. Family oriented life-style; abundant recreation, good schools, restaurants, shopping. Beautiful homes close to office and hospital are reasonably priced. Easy access to metropolitan and resort areas. California license required. Contact Tulare District Hospital Physician Recruiting Office, PO Box 90112, Los Angeles, CA 90009; (800) 468-2687.

ACADEMIC INTERNISTS. The University of Nevada School of Medicine is seeking BC/BE Academic Internists for faculty positions in Reno and Las Vegas. Applicants will be responsible for teaching General Internal Medicine to medical students and residents in a community integrated medical school setting. Research experience or interest is required. Rank dependent upon qualifications. Must be eligible for licensure in Nevada. Send CV and names of three references to Stanley Shane, MD, University of Nevada School of Medicine, Reno, NV 89557. Search will continue until positions filled. AA/EOE.

LOS ANGELES. Small multispecialty group seeks second Pediatrician and OB/GYN to work with present physicians. Excellent compensation and benefits. Looking for long term partners. Call or send CV to Craig Kaner, All Care Medical Group, 2675 E. Slauson Ave, Huntington Park, CA 90255; (213) 589-6681.

EUGENE CLINIC, EUGENE, OREGON

Dynamic 55 physician multispecialty group with seven locations seeks BC/BE physicians in the following specialties: Family Practice, Geriatrics, Occupational Medicine, Orthopedics, Psychiatry, Urgency Care, Urology. Eugene, attractive university town within 60 mile radius of Cascade Mountains and Oregon coast, offers superlative life-style, fine school system, active and varied cultural opportunities, and unlimited recreation. Qualified candidates send CV and three letters of reference to:

Physician Recruiter
1162 Willamette St
Eugene, OR 97401

BC/BE FAMILY PRACTITIONER, CALIFORNIA. Position offers excellent salary ($84,100 to $102,600) plus comprehensive benefit package in desirable central California location. Multispecialty group practice sponsored by County with all inpatient work done in private hospitals. Located near Sequoia National Park. Family oriented life-style; abundant recreation, good schools, restaurants, shopping. Beautiful homes close to office and hospital are reasonably priced. Easy access to metropolitan and resort areas. California license required. Contact Tulare District Hospital Physician Recruiting Office, PO Box 90112, Los Angeles, CA 90009; (800) 468-2687.

GERIATRICIAN/INTERNIST. We are seeking a BC Internist with Geriatric training or certification to join a group of two to practice Geriatric Medicine, actively participate in a university-affiliated teaching program, and assist in program development. Competitive salary and excellent fringe benefits. Send CV to Gary Steinke, MD, Santa Clara Valley Medical Center, 750 S. Bascom Ave, San Jose, CA 95128.

FAMILY PRACTICE OPPORTUNITY. East Central Arizona community close to snow skiing, boating, fishing, and big game hunting. Excellent compensation package, flexible hours, and potential for partnership. Send CV or call Robert Evans, Jackson and Coker, Inc, 115 Perimeter Center Pl, Ste 380 WJM0, Atlanta, GA 30346; 1 (800) 544-1987.

SACRAMENTO AREA. Immediate opening for BC/BE Family Practice Physician to join busy seven member group. Guaranteed salary and excellent benefit package. Partnership offered after two years. Opportunity to practice full range of primary medicine including Pediatrics, Geriatrics, and inpatient care. Excellent community to practice medicine with affordable housing, excellent schools, and state of the art hospital facilities. Send CV to Craig Lyon, 1219 30th St, Sacramento, CA 95816; (916) 737-0226.

DON'T FORGET!

The deadline for submitting classifieds for the November issue of WJM is September 25. Send your advertisement to:

Classified Advertising
WJM, PO Box 7602
San Francisco, CA 94120-7602
(415) 541-0900, ext 476

(Continued on Page 349)

(Continued from Page 348)

ORTHOPEDIC SURGEON

BC Orthopedic Surgeon needed for office practice in beautiful southern California area. Full- or part-time, surgery optional. Excellent compensation package. Send CV to **Ronald Gilbert, MD, c/o Gilbert Medical Group, 1076 E. First St, #A, Tustin, CA 92680; or call (714) 832-1516.**

SOUTHERN CALIFORNIA

Upscale, family oriented community in the eastern foothills of Los Angeles County offers qualified primary care physicians (Family Practice, General Internist, Pediatricians) both group and private practice opportunities. Complete compensation package includes salary guarantees, practice management and marketing support, malpractice, and relocation expense reimbursement. BC/BE. Excellent growth potential. Send CV to Gary May, Foothill Presbyterian Hospital, 250 S. Grand Ave, Glendora, CA 91740; or call (818) 963-8411.

ESTABLISHED RESEARCH CLINICS FOR SALE

to licensed physician(s); outstanding opportunity; western part of Washington State; asking $850,000, terms possible; principals only. Contact **Robert Reeves, MD, 140 N. Percival St, Olympia, WA 98502.**

SAN DIEGO COUNTY. Family, Internal, OB/GYN and Pediatric practices available. Long established—doctors retiring. Various prices and low down payments. Call CBI, San Diego County's professional practice sales specialists, (619) 283-7009.

OB/GYN NORTH HOLLYWOOD—High gross, low overhead. All private patient. Twenty-five-year practice. Will refer all OB and major GYN now. To retire December 1991. Room to start now. Call Sandy (805) 524-1013. Nurse will stay.

HAYWARD. Fully equipped office for sale or rent to Internist or Pulmonologist. Practice based on therapy which has always relieved asthma and COPD during past 30 years. Contact J. J. Robbins, MD, 1634 B St, Hayward, CA 94541; or (415) 581-3451.

DENVER'S CHERRY CREEK GROWTH AREA. Medical Suite—Three exams; one consult; business area; RR; 874 square feet. Ophthalmology Suite—Two large connecting refracting lanes; lens room; lab; office; business area; RR; 1,177 square feet. Pediatric Suite—Five exams; two consults; lab; business area; RR; 1,500 square feet. (Available January 1, 1991.) Well located; abundant parking; generous tenant finish allowance. Contact Sid Hendry (303) 329-0855.

PRACTICE AVAILABLE IN THE LAND OF ENCHANTMENT, extraordinary Santa Fe, New Mexico. Thriving General Practice, subspecializing in pain management. Goodwill, equipment, accounts receivable negotiable. (505) 438-6299.

PEDIATRIC PRACTICE FOR SALE, central California. Very well established busy Pediatric office. Well equipped and staffed. Gross over 200K with growth potential. Close to two hospitals. Beautiful city with affordable housing and lots of recreational activities. Near Sequoia mountains. Two hours from coast. For details call (209) 734-0161 after 6:00 pm.

INTERNAL MEDICINE—San Diego City, high development area. Gross $160,000. Low overhead with high net cash flow. Contact Practice Consultants. (619) 528-2321, Dr Bernard Press, Broker.

NORTHERN AND CENTRAL CALIFORNIA. Established practices available: Dermatology, ENT, Family, Internal Medicine, GYN, Pediatrics, Personal Injury, Plastic Surgery, Urology. Reasonable terms and prices. Call/write Bradshaw Associates, 21 Altamount, Orinda, CA 94563; (415) 376-0762, FAX (415) 376-0813.

ESTABLISHED FAMILY PRACTICE for sale in Cody, Wyoming. Purchase price of $180,000 includes a 1,735 square foot building designed for dual practice. Owner financing available. Call Brokerage West, (307) 587-6234.

SAN DIEGO COUNTY GERIATRIC/PRIMARY CARE. In pleasant north coastal town. Reasonable. Retiring. Can aid transition to well established practice with stable patient population. Office, equipment available for lease. Call (619) 434-1053.

NURSE PRACTITIONERS, PHYSICIAN ASSISTANTS, NURSE MIDWIVES. We provide the right mid-level professional for your clinical setting. Western Practitioner Resources, Heidi Bourne, RN, Director. (800) 345-5859 or (707) 839-5859.

GROWTH AREA OF SANTA CLARA VALLEY. New medical office space for lease in the growth area of Silicon Valley, Morgan Hill, California. Easy access, abundant parking, well located, generous tenant improvement allowances. Excellent patient referral sources. Contact Dr Jon Hatakeyama, (408) 779-7391.

LOST LEASE. Selling exam tables, lights, blood chemistry analyzers, Min x-ray, reception room furniture, chairs, IBM typewriter, cabinetry. New, some used. Also new computers. Call (408) 659-4828 NOW.

G.E. FLUORO/X-RAY UNIT. Includes front load spot film device, wall unit, grid, spare tube, accessories. For more information call (415) 463-1000.

PATHOLOGIST—Desires relocation in Northwest or Nevada. BC in AP-CP, Dermpath and Immunopath. Experienced director of busy large lab. Used to heavy surgical Path load. Prefers surgical Path. Inquiries to Number 220, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

LOCUM TENENS

"Quality coverage by proven professionals"

INTERIM *Physicians* NETWORK

Six regional offices
West of the Mississippi:
New Braunfels, Texas
Phoenix, Arizona
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1-800-531-1122

WESTERN PHYSICIANS REGISTRY

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Permanent Placement

Since 1980, WPR has served the needs of California's physicians. When someone needs coverage or ongoing, part-time help, we find the right physician. When a practice must expand, we find a permanent associate. We pride ourselves on our discretion, our very personal service matching the right person with the right job. We work only in California, concentrating our efforts where we know our market. Our clients include private practices, HMOs, urgent care centers, emergency departments, multispecialty groups, and community clinics.

Northern California
Jim Ellis, Director
(415) 673-7676 or (800) 437-7676

Southern California
Tracy Zweig, Director
(805) 643-9346 or (800) 635-3175

Ads Get Results!

CLASSIFIED ADVERTISING INFORMATION

(415) 541-0900, Ext 476

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NOTICE TO WJM CLASSIFIED DISPLAY ADVERTISERS

The column width for WJM classified display advertisements has been changed to 2 1/8 inches (from 2 1/4 inches). Any new camera ready material should fit into a 2 1/8 inch column. Call with any questions; (415) 541-0900, ext 476.

CONFERENCES

Fifth Annual Central Oregon Oncology Conference on:

THE BRAIN AND CANCER: SCIENCE AND PSYCHOLOGY

January 31-February 2, 1991

Inn of the Seventh Mountain, Bend, Oregon

Co-sponsored by St. Charles Medical Center, Bend, Oregon; The Oregon Health Sciences University, Portland Oregon; The American Cancer Society, The Oregon Division

For further information, contact:

Lois Gibson, St. Charles Medical Center
2500 NE Neff Rd, Bend, OR 97701
(503) 382-4321

COURSES

SKI—CME EUROPE or HELI-B.C. $25.00. Rainier Educational Emprize. T. Akamatsu, MD, 502 N. Stadium Way, Tacoma, WA 98403; (206) 572-4619.

CONTINUING MEDICAL EDUCATION COURSE FOR PRIMARY PHYSICIANS

October 24, 25, 26, 1990
VANCOUVER, B.C.

CONTACT:
Medical Services, St. Paul's Hospital
1081 Burrard Street, Vancouver, B.C.
V6Z 1Y6. (604) 682-2344, ext 2721

ATTENTION WJM CLASSIFIED ADVERTISERS

The phone extension for WJM classified advertising has been changed to 476.
The complete number for Classifieds is now (415) 541-0900, ext 476.

Just a fraction of what we spend dining out could help pick up the tab for a good cause.

It's so easy to help your community, when you think about it.

Millions of people have helped make five percent of their incomes and five hours of volunteer time per week the standard of giving in America.

Get involved with the causes you care about and give five.

Give Five. What you get back is immeasurable.

The Western Journal of Medicine

SINCE 1902 • CIRCULATION 56,000+

Classified Advertisements

The rate for each insertion is **$7 per line** (average six words per line) **with five line [$35] minimum.** A confidential box number (in lieu of your address) can be assigned to your advertisement for $5 each month. The replies to the box number will be directly forwarded to you as they arrive at *WJM*'s office.

Classified display rates $50 per inch. Maximum sizes: 1 column by 9½ inches or 2 columns by 5 inches (2⅛ inches per column). Larger classified ad space by special arrangements.

Copy for classified advertisements should be received not later than **25th of the second month preceding issue. All copy must be typed or printed.** • Classified advertisers using Box Numbers forbid the disclosure of their identity; your inquiries in writing will be forwarded to Box Number advertisers. The right is reserved to reject, withdraw, or modify all classified advertising copy in conformity with the decisions of the Advertising Committee.

Please Type or Print Advertising Copy

Classified Advertisements Are Payable in Advance

THE WESTERN JOURNAL OF MEDICINE
P.O. BOX 7602, SAN FRANCISCO, CA 94120-7602
(415) 541-0900 EXT. 476

ad copy

Print or Type Clearly

Number of lines _____ × $7 = $_____

Optional: Confidential box number charge + $5 = _____

Subtotal (minimum $35 *or* minimum $40 with confidential box number) _____

Number of insertions _____ × $_____ = (subtotal)

Check enclosed for: $_____

Name (Please Print) _____

Contact _____

Address _____

City/State/Zip _____

(____) Phone _____

Signature _____

WESTERN STATE MEDICAL ASSOCIATIONS' MEETINGS

Alaska State Medical Association—2401 E 42nd Ave, Suite 104, Anchorage 99508. (907) 562-2662. Annual Meeting: 1991, date and location to be announced.

Arizona Medical Association, Inc—810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: 1991, date and location to be announced.

California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 8-13, 1991, Bally's Grand Hotel, Reno.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 13-16, 1990, Keystone.

Hawaii Medical Association—1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: October 12-14, 1990, Ilikai, Honolulu.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: 1991, date and location to be announced.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 4-6, 1990, Sheraton, Billings.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: 1991, date and location to be announced.

New Mexico Medical Society—7770 Jefferson, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: 1991, date and location to be announced.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting (House of Delegates only): 1991, date and location to be announced.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 12-14, 1990, Marriott Hotel, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: September 20-23, 1990, Sheraton, Spokane.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: 1991, date and location to be announced.

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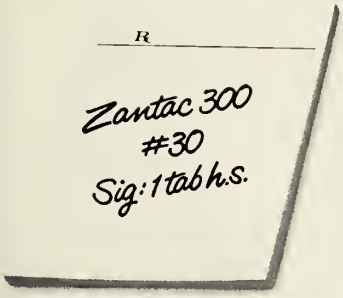
In active duodenal ulcers

Once-a-night h.s. therapy controls acid rain

Zantac® 300
ranitidine HCl/Glaxo 300 mg tablets



Zantac® 150 Tablets
(ranitidine hydrochloride)
Zantac® 300 Tablets
(ranitidine hydrochloride)
Zantac® Syrup
(ranitidine hydrochloride)

BRIEF SUMMARY

The following is a brief summary only. Before prescribing, see complete prescribing information in Zantac® product labeling.

INDICATIONS AND USAGE: Zantac® is indicated in:

1. Short-term treatment of **active duodenal ulcer**. Most patients heal within four weeks.
2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathological hypersecretory conditions** (eg,Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of **active, benign gastric ulcer.** Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated.
5. Treatment of **gastroesophageal reflux disease (GERD).** Symptomatic relief commonly occurs within one or two weeks after starting therapy. Therapy for longer than six weeks has not been studied.

In active duodenal ulcer, active, benign gastric ulcer, hypersecretory states, and GERD, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: Zantac® is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS: General: 1. Symptomatic response to Zantac® therapy does not preclude the presence of gastric malignancy.

2. Since Zantac is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since Zantac is metabolized in the liver.

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during Zantac therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although Zantac has been reported to bind weakly to cytochrome P-450 *in vitro*, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions that suggest that Zantac may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2,000 mg/kg/d.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, Escherichia coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

Pregnancy: ***Teratogenic Effects: Pregnancy Category B.*** Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Zantac. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Zantac is secreted in human milk. Caution should be exercised when Zantac is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with Zantac®. The relationship to Zantac therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to Zantac administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported.

Cardiovascular: As with other H_2-blockers, rare reports of arrhythmias such as tachycardia, bradycardia, atrioventricular block, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, abdominal discomfort/pain, and rare reports of pancreatitis.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid intravenously for seven days, and in 4 of 24 subjects receiving 50 mg qid intravenously for five days. With oral administration there have been occasional reports of hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice. These were usually reversible.

Musculoskeletal: Rare reports of arthralgias.

Hematologic: Blood count changes (leukopenia, granulocytopenia, thrombocytopenia) have occurred in a few patients. These were usually reversible. Rare cases of agranulocytosis, pancytopenia, sometimes with marrow hypoplasia, and aplastic anemia have been reported.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by Zantac and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when Zantac has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving Zantac, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia), anaphylaxis, angioneurotic edema, and small increases in serum creatinine.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: (See complete prescribing information in Zantac® product labeling.)

Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice daily. An alternate dosage of 300 mg or 20 ml (4 teaspoonfuls equivalent to 300 mg of ranitidine) once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.

Maintenance Therapy: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day. In some patients it may be necessary to administer Zantac® 150-mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/d have been employed in patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day.

GERD: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day.

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with Zantac, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg or 10 ml (equivalent to 150 mg of ranitidine) every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: Zantac® 300 Tablets (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 (NDC 0173-0393-40) tablets and unit dose packs of 100 (NDC 0173-0393-47) tablets.

Zantac® 150 Tablets (ranitidine hydrochloride equivalent to 150 mg of ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 60 (NDC 0173-0344-42) and 100 (NDC 0173-0344-09) tablets and unit dose packs of 100 (NDC 0173-0344-47) tablets.

Store between 15° and 30° C (59° and 86° F) in a dry place. Protect from light. Replace cap securely after each opening.

Zantac® Syrup, a clear, peppermint-flavored liquid, contains 16.8 mg of ranitidine hydrochloride equivalent to 15 mg of ranitidine per 1 ml in bottles of 16 fluid ounces (one pint) (NDC 0173-0383-54).

Store between 4° and 25° C (39° and 77° F). Dispense in tight, light-resistant containers as defined in the USP/NF.

January 1990

Glaxo Pharmaceuticals™
DIVISION OF GLAXO INC.
Research Triangle Park, NC 27709

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CONTROL ACID RAIN

with once-a-night h.s. therapy for active duodenal ulcers

Zantac® 300

ranitidine HCl/Glaxo 300 mg tablets

Glaxo / ROCHE

See adjacent page for Brief Summary of Product Information

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OF MEDICINE
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The Western Journal of Medicine

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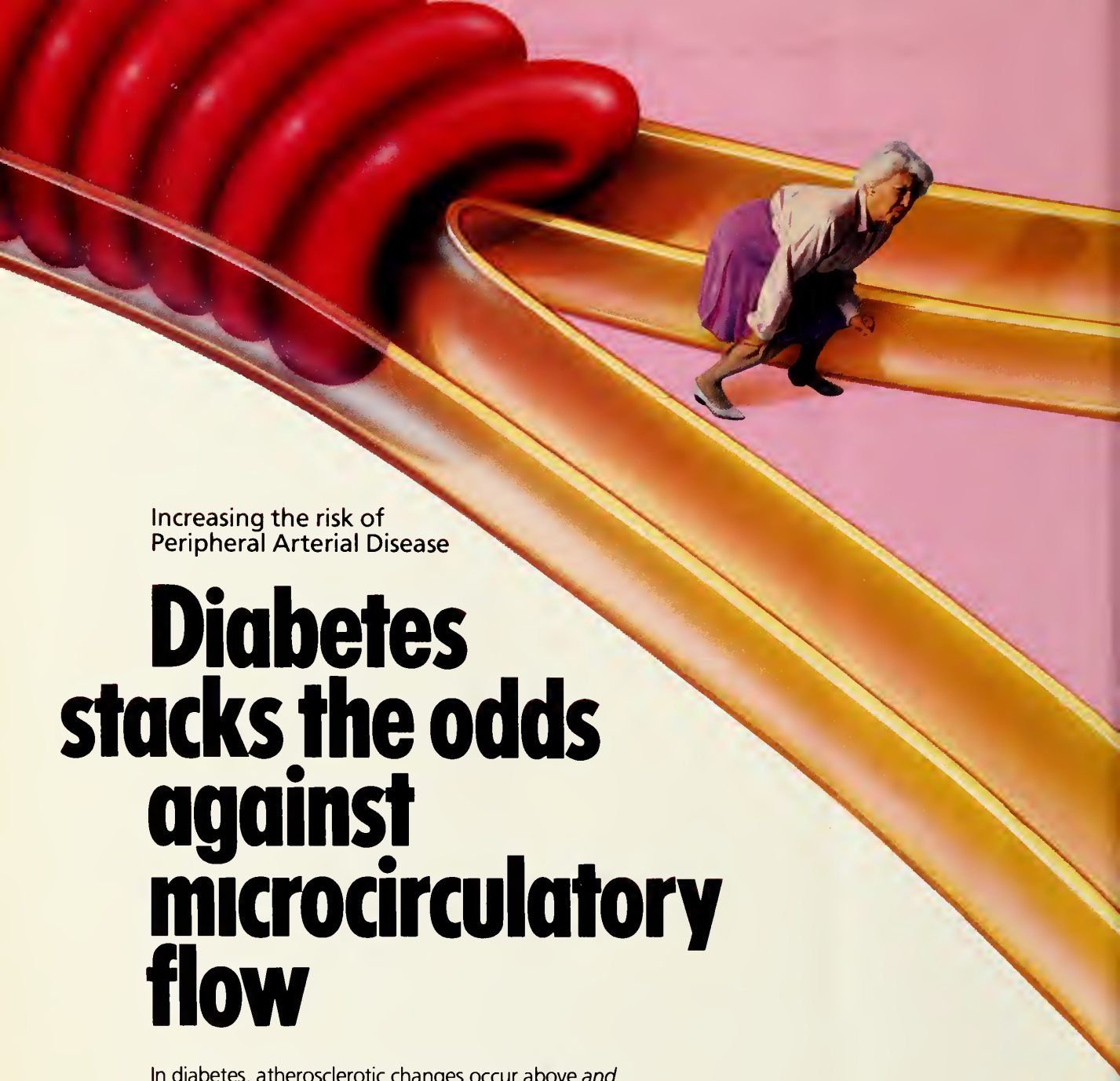

Increasing the risk of
Peripheral Arterial Disease

Diabetes stacks the odds against microcirculatory flow

In diabetes, atherosclerotic changes occur above *and* below the knee, often involving smaller vessels and multisegmental occlusions.[1] Diabetes has also been *associated* with decreased red cell flexibility, and increasing fibrinogen levels, platelet aggregation and platelet adherence, factors which predispose patients to peripheral arterial disease.[1]

Duration of Diabetes	Incidence of PAD
10 years	15%
20 years	45%

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Now Medi-Cal approved
for patients with diabetes who have been diagnosed as having intermittent claudication
Drug Type Code: 5041AHE

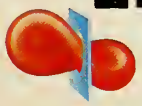
Trental® improves microcirculatory flow and lifestyle for many diabetics with PAD

Trental® (pentoxifylline) increases red cell flexibility[2] while decreasing elevated plasma fibrinogen levels,[3] aggregation of platelets[4] and red cells.[5] The resulting increase in microcirculatory flow enhances tissue perfusion and oxygenation.[6]

With Trental, patients experience significant improvement in pain-free walking distance, paresthesia, skin temperature and subjective overall response.[7]

Not a vasodilator • Not an anticoagulant • Not related to aspirin or dipyridamole

Trental® 400 mg Tablets
(pentoxifylline)



The only proven-effective agent for intermittent claudication, a symptom of peripheral arterial disease

Please see references and brief summary of prescribing information on following page.

Trental® can improve function and symptoms, but is not intended to replace more definitive therapy, such as surgery.

References:
1. Levin ME, Sicard GA: Evaluating and treating diabetic peripheral vascular disease, Part I. *Clinical Diabetes* May/Jun 1987. **2.** Stormer B, Kleinschmidt K, Loose D, et al: Rheological changes in the blood of patients with chronic arterial occlusive disease after the administration of vasoactive drugs. *Curr Med Res Opin* 1977;4:588-595. **3.** Perego MA, Sergio G, Artale F: Haemorrheological aspects of the pathophysiology and clinical features of peripheral occlusive arterial disease. *Pharmatherapeutica* 1983;3(1):91. **4.** Seiffge D: *IRCS Med Sci* 1980;8:727. **5.** Lowe GDO, Drummond MM, Forbes CD, et al: Blood and plasma viscosity in prediction of venous thrombosis. Abstracts: 77, International Symposium on Filterability and Red Blood Cell Deformability, Göteborg, Sweden, Sep 11-13, 1980. **6.** Ehrly AM: Effects of orally administered pentoxifylline on muscular oxygen pressure in patients with intermittent claudication. *IRCS Med Sci* 1982;10:401. **7.** Schubotz R: Double-blind trial of pentoxifylline in diabetes with peripheral vascular disorders. *Pharmatherapeutica* 1976;1(3):172-179.

Trental® (pentoxifylline) Tablets, 400 mg
A brief summary of the Prescribing Information follows.

INDICATIONS AND USAGE:
Trental® (pentoxifylline) is indicated for the treatment of patients with intermittent claudication on the basis of chronic occlusive arterial disease of the limbs. Trental® (pentoxifylline) can improve function and symptoms but is not intended to replace more definitive therapy, such as surgical bypass, or removal of arterial obstructions when treating peripheral vascular disease.

CONTRAINDICATIONS:
Trental® (pentoxifylline) should not be used in patients who have previously exhibited intolerance to this product or methylxanthines such as caffeine, theophylline, and theobromine.

PRECAUTIONS:
General: Patients with chronic occlusive arterial disease of the limbs frequently show other manifestations of arteriosclerotic disease. Trental® (pentoxifylline) has been used safely for treatment of peripheral arterial disease in patients with concurrent coronary artery and cerebrovascular diseases, but there have been occasional reports of angina, hypotension, and arrhythmia. Controlled trials do not show that Trental® (pentoxifylline) causes such adverse effects more often than placebo, but, as it is a methylxanthine derivative, it is possible some individuals will experience such responses.
Drug Interactions: Although a causal relationship has not been established, there have been reports of bleeding and/or prolonged prothrombin time in patients treated with Trental® (pentoxifylline) with and without anticoagulants or platelet aggregation inhibitors. Patients on warfarin should have more frequent monitoring of prothrombin times, while patients with other risk factors complicated by hemorrhage (e.g., recent surgery, peptic ulceration) should have periodic examinations for bleeding including hematocrit and/or hemoglobin. Trental® (pentoxifylline) has been used concurrently with antihypertensive drugs, beta blockers, digitalis, diuretics, antidiabetic agents, and antiarrhythmics, without observed problems. Small decreases in blood pressure have been observed in some patients treated with Trental® (pentoxifylline); periodic systemic blood pressure monitoring is recommended for patients receiving concomitant antihypertensive therapy. If indicated, dosage of the antihypertensive agents should be reduced.
Carcinogenesis, Mutagenesis and Impairment of Fertility: Long-term studies of the carcinogenic potential of pentoxifylline were conducted in mice and rats by dietary administration of the drug at doses up to approximately 24 times (570 mg/kg) the maximum recommended human daily dose (MRHD) of 24 mg/kg for 18 months in mice and 18 months in rats with an additional 6 months without drug exposure in the latter. No carcinogenic potential for pentoxifylline was noted in the mouse study. In the rat study, there was a statistically significant increase in benign mammary fibroadenomas in females in the high dose group (24 × MRHD). The relevance of this finding to human use is uncertain since this was only a marginal statistically significant increase for a tumor that is common in aged rats. Pentoxifylline was devoid of mutagenic activity in various strains of *Salmonella* (Ames test) when tested in the presence and absence of metabolic activation.
Pregnancy: Category C. Teratogenic studies have been performed in rats and rabbits at oral doses up to about 25 and 10 times the maximum recommended human daily dose (MRHD) of 24 mg/kg, respectively. No evidence of fetal malformation was observed. Increased resorption was seen in rats at 25 times MRHD. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Trental® (pentoxifylline) should be used during pregnancy only if clearly needed.
Nursing Mothers: Pentoxifylline and its metabolites are excreted in human milk. Because of the potential for tumorigenicity shown for pentoxifylline in rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.
Pediatric Use: Safety and effectiveness in children below the age of 18 years have not been established.

ADVERSE REACTIONS:
Clinical trials were conducted using either controlled-release Trental® (pentoxifylline) tablets for up to 60 weeks or immediate-release Trental® (pentoxifylline) capsules for up to 24 weeks. Dosage ranges in the tablet studies were 400 mg bid to tid and in the capsule studies, 200-400 mg tid.
The table summarizes the incidence (in percent) of adverse reactions considered drug related, as well as the numbers of patients who received controlled-release Trental® (pentoxifylline) tablets, immediate-release Trental® (pentoxifylline) capsules, or the corresponding placebos. The incidence of adverse reactions was higher in the capsule studies (where dose related increases were seen in digestive and nervous system side effects) than in the tablet studies. Studies with the capsule include domestic experience, whereas studies with the controlled-release tablets were conducted outside the U.S. The table indicates that in the tablet studies few patients discontinued because of adverse effects.

INCIDENCE (%) OF SIDE EFFECTS

	Controlled-Release Tablets		Immediate-Release Capsules	
	Commercially Available		Used only for Controlled Clinical Trials	
	Trental®	Placebo	Trental®	Placebo
(Numbers of Patients at Risk)	(321)	(128)	(177)	(138)
Discontinued for Side Effect	3.1	0	9.6	7.2
CARDIOVASCULAR SYSTEM				
Angina/Chest Pain	0.3	—	1.1	2.2
Arrhythmia/Palpitation	—	—	1.7	0.7
Flushing	—	—	2.3	0.7
DIGESTIVE SYSTEM				
Abdominal Discomfort	—	—	4.0	1.4
Belching/Flatus/Bloating	0.6	—	9.0	3.6
Diarrhea	—	—	3.4	2.9
Dyspepsia	2.8	4.7	9.6	2.9
Nausea	2.2	0.8	28.8	8.7
Vomiting	1.2	—	4.5	0.7
NERVOUS SYSTEM				
Agitation/Nervousness	—	—	1.7	0.7
Dizziness	1.9	3.1	11.9	4.3
Drowsiness	—	—	1.1	5.8
Headache	1.2	1.6	6.2	5.8
Insomnia	—	—	2.3	2.2
Tremor	0.3	0.8	—	—
Blurred Vision	—	—	2.3	1.4

Trental® (pentoxifylline) has been marketed in Europe and elsewhere since 1972. In addition to the above symptoms, the following have been reported spontaneously since marketing or occurred in other clinical trials with an incidence of less than 1%; the causal relationship was uncertain:
Cardiovascular—dyspnea, edema, hypotension.
Digestive—anorexia, cholecystitis, constipation, dry mouth/thirst.
Nervous—anxiety, confusion.
Respiratory—epistaxis, flu-like symptoms, laryngitis, nasal congestion.
Skin and Appendages—brittle fingernails, pruritus, rash, urticaria, angioedema.
Special Senses—blurred vision, conjunctivitis, earache, scotoma.
Miscellaneous—bad taste, excessive salivation, leukopenia, malaise, sore throat/swollen neck glands, weight change.
A few rare events have been reported spontaneously worldwide since marketing in 1972. Although they occurred under circumstances in which a causal relationship with pentoxifylline could not be established, they are listed to serve as information for physicians: Cardiovascular—angina, arrhythmia, tachycardia; Digestive—hepatitis, jaundice, increased liver enzymes; and Hemic and Lymphatic—decreased serum fibrinogen, pancytopenia, aplastic anemia, purpura, thrombocytopenia.

OVERDOSAGE:
Overdosage with Trental® (pentoxifylline) has been reported in children and adults. Symptoms appear to be dose related. A report from a poison control center on 44 patients taking overdoses of enteric-coated pentoxifylline tablets noted that symptoms usually occurred 4-5 hours after ingestion and lasted about 12 hours. The highest amount ingested was 80 mg/kg; flushing, hypotension, convulsions, somnolence, loss of consciousness, fever, and agitation occurred. All patients recovered.
In addition to symptomatic treatment and gastric lavage, special attention must be given to supporting respiration, maintaining systemic blood pressure, and controlling convulsions. Activated charcoal has been used to adsorb pentoxifylline in patients who have overdosed.

DOSAGE AND ADMINISTRATION:
The usual dosage of Trental® (pentoxifylline) in controlled-release tablet form is one tablet (400 mg) three times a day with meals.
While the effect of Trental® (pentoxifylline) may be seen within 2 to 4 weeks, it is recommended that treatment be continued for at least 8 weeks. Efficacy has been demonstrated in double-blind clinical studies of 6 months duration.
Digestive and central nervous system side effects are dose related. If patients develop these side effects it is recommended that the dosage be lowered to one tablet twice a day (800 mg/day). If side effects persist at this lower dosage, the administration of Trental® (pentoxifylline) should be discontinued. Edition 2/88
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Somerville, New Jersey 08876-1258

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Trental® 400 mg Tablets
(pentoxifylline)

The only proven-effective agent for intermittent claudication, a symptom of peripheral arterial disease

Q73224-790

The results are worth waiting for.

Patience pays off when you start a patient on Trental®

Trental® therapy can make a dramatic difference to your patients – increasing their mobility and independence, enhancing their participation in social and professional activities, and giving them a fresh outlook on life. But, the physical improvement behind these benefits doesn't happen overnight. It's a gradual process.

3x3=success with Trental® treatment

To start patients off on the right foot with Trental®, follow the 3×3 formula for success.

3 tablets a day, with meals

The usual dosage of Trental® is one 400 mg tablet taken 3 times a day, with a full meal.

3-month initial trial, evaluate, then continue

While patients might feel somewhat better within weeks, at least 3 months' therapy is generally required before the full effectiveness of Trental® becomes evident. To sustain improvement, therapy must be continued.

Trental® 400 mg Tablets

(pentoxifylline)

The only proven-effective agent for intermittent claudication—a symptom of peripheral arterial disease

The Western Journal of Medicine®

SINCE 1902 ISSN 0093-0415

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"Information for Authors"—A complete guide to manuscript submission and *WJM* style appears in the January and July issues. Manuscripts may be prepared in accordance with the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" (*Annals of Internal Medicine*, Feb 1988; *The Medical Journal of Australia*, Feb 1988).

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The Western Journal of Medicine

(ISSN 0093-0415/USPS 084 480) is published monthly for $35 per year (USA and Canada) by the California Medical Association, 221 Main Street, San Francisco, CA 94105. Second-class postage paid at San Francisco and additional mailing offices.

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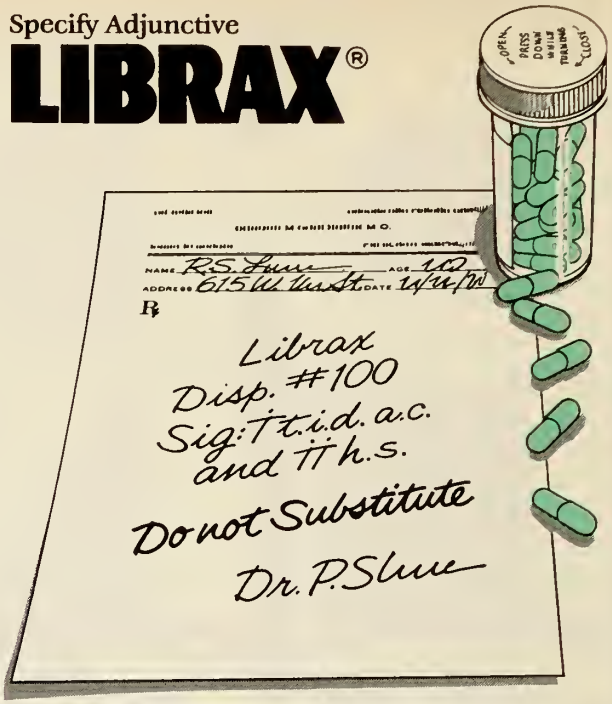

Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium bromide.

Please consult complete prescribing information, a summary of which follows:

* **Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:
"Possibly" effective: as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.
Final classification of the less-than-effective indications requires further investigation.

Contraindications: Glaucoma; prostatic hypertrophy, benign bladder neck obstruction; hypersensitivity to chlordiazepoxide HCl and/or clidinium Br.
Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants, and against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).
Usage in Pregnancy: Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.
As with all anticholinergics, inhibition of lactation may occur.
Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).
Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established. Inform patients to consult physician before increasing dose or abruptly discontinuing this drug.
Adverse Reactions: No side effects or manifestations not seen with either compound alone reported with Librax. When chlordiazepoxide HCl is used alone, drowsiness, ataxia, confusion may occur, especially in elderly and debilitated; avoidable in most cases by proper dosage adjustment, but also occasionally observed at lower dosage ranges. Syncope reported in a few instances. Also encountered: isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent, generally controlled with dosage reduction; changes in EEG patterns may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice, hepatic dysfunction reported occasionally with chlordiazepoxide HCl, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax typical of anticholinergic agents, *i.e.*, dryness of mouth, blurring of vision, urinary hesitancy, constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.
Drug Abuse and Dependence: Withdrawal symptoms similar to those noted with barbiturates and alcohol have occurred following abrupt discontinuance of chlordiazepoxide; more severe seen after excessive doses over extended periods, milder after taking continuously at therapeutic levels for several months. After extended therapy, avoid abrupt discontinuation and taper dosage. Carefully supervise addiction-prone individuals because of predisposition to habituation and dependence.

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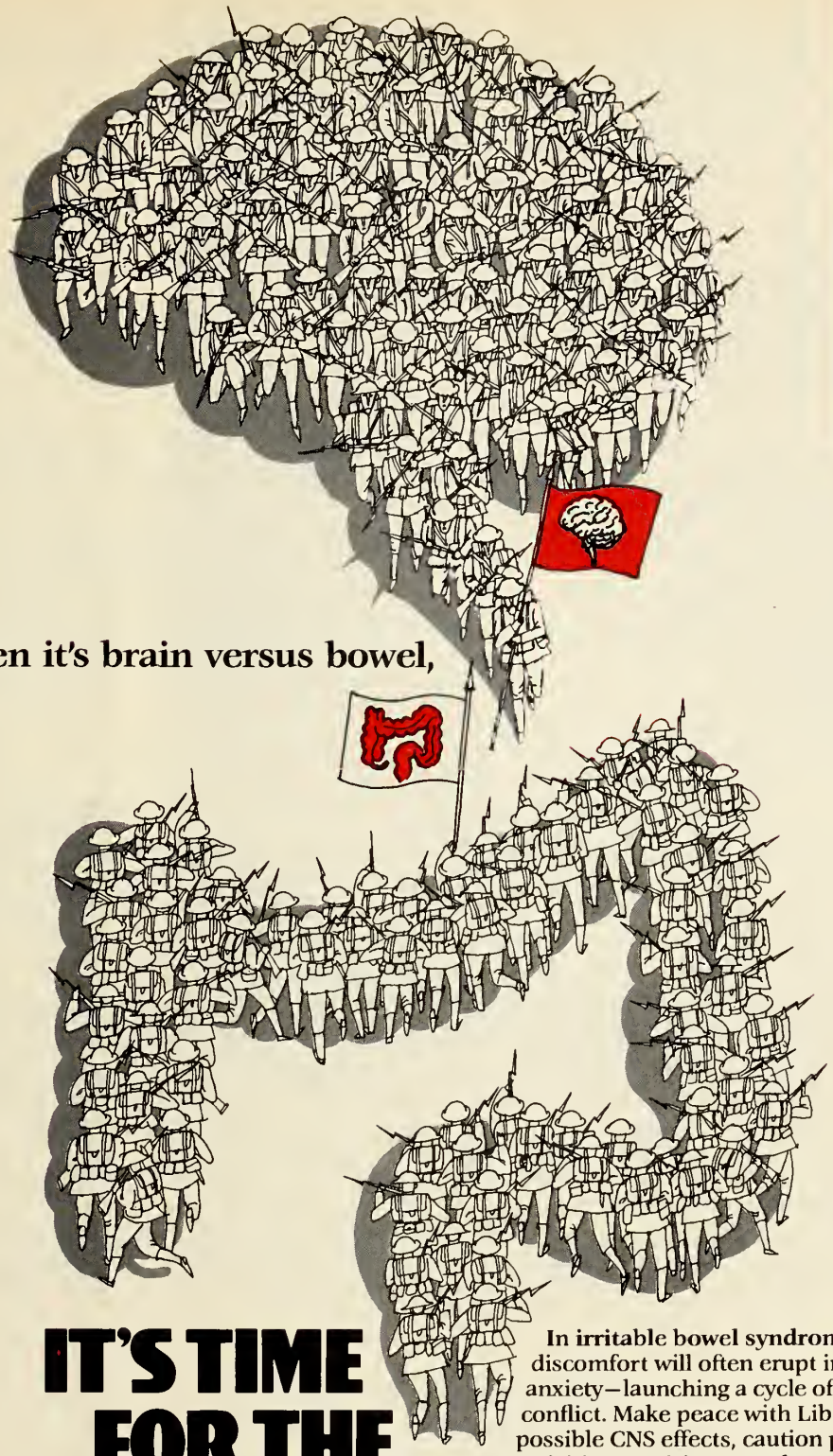

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From the Pulmonary Division, Departments of Medicine and Radiology, Doctor's Hospital of Lokewood, and the Reider Laser Center, Memorial Medical Center of Long Beach, California, and University of California, Los Angeles, School of Medicine; the Departments of Radiological Sciences and Pulmonary/Critical Care Medicine, University of California, Los Angeles, School of Medicine; and the Department of Radiology, New York University Medical Center, Bellevue Hospital, New York.

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From the Office of AIDS, California Department of Health Services (CDHS), Sacramento, and the Viral and Rickettsial Disease Laboratory, CDHS, Berkeley. Dr Kizer is the Director of CDHS. Dr Trachtenberg is now with the Institute for Health Policy Studies, University of California, San Francisco, School of Medicine.

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MICHAEL SCHEIBER, MD, MPH, and NEAL HALFON, MD, MPH

From University of California, Berkeley-University of California, San Francisco, School of Medicine, Joint Medical Program and the Center for the Vulnerable Child, Children's Hospital Medical Center of Northern California, Oakland, and the Institute for Health Policy Studies, University of California, San Francisco, School of Medicine.

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Discussant: HARLAN E. IVES, MD, PhD

A discussion selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from a transcription, it was edited by Homer A. Boushey, MD, Professor of Medicine, and Nathan M. Bass, MD, PhD, Associate Professor of Medicine, under the direction of Lloyd H. Smith, Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine.

(Continued on Page 364)

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but she's alert,
functioning, and
at no risk of a
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withdrawal
syndrome when
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BuSpar relieves anxiety and returns your patient to normal activity

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...without producing a benzodiazepine withdrawal syndrome[3] upon discontinuation

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for a different kind of calm

*Because the effects of BuSpar in any individual patient may not be predictable, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that BuSpar treatment does not affect them adversely.

For Brief Summary, please see following page.

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BuSpar® (buspirone HCl)

References: 1. Newton RE, *et al.* A review of the side effect profile of buspirone. *Am J Med* 1986;80(3B):17-21. 2. Lucki I, *et al.* Differential effects of the anxiolytic drugs, diazepam and buspirone, on memory function. *Br J Clin Pharmacol* 1987;23:207-211. 3. Lader M. Assessing the potential for buspirone dependence or abuse and effects of its withdrawal. *Am J Med* 1987;82(5A):20-26.

Contraindications: Hypersensitivity to buspirone hydrochloride.

Warnings: The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. Since blood pressure has become elevated when BuSpar was administered concomitantly with an MAOI, such concomitant use is not recommended. BuSpar should not be employed in lieu of appropriate antipsychotic treatment.

Precautions: ***General***—*Interference with cognitive and motor performance:* Although buspirone is less sedating than other anxiolytics and does not produce significant functional impairment, its CNS effects in a given patient may not be predictable; therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone does not affect them adversely. Although buspirone has not been shown to increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use with alcohol.

Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug dependent patients: Because buspirone will not block the withdrawal syndrome often seen with cessation of therapy with benzodiazepines and other common sedative/hypnotic drugs, before starting buspirone withdraw patients gradually from their prior treatment, especially those who used a CNS depressant chronically. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug and its elimination half-life. The withdrawal syndrome can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

Possible concerns related to buspirone's binding to dopamine receptors: Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (eg, dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported; the syndrome may be due to increased central noradrenergic activity or may be attributable to dopaminergic effects (ie, represent akathisia).

Information for Patients—Patients should be instructed to inform their physician about any medications, prescription or nonprescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone; to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone; to inform their physician if they are breast feeding; and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them.

Drug Interactions—Concomitant use with other CNS active drugs should be approached with caution (see **Warnings**). Concomitant use with trazodone may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients. Concomitant administration of BuSpar and haloperidol resulted in increased serum haloperidol concentrations in normal volunteers. The clinical significance is not clear. Buspirone does not displace tightly bound drugs like phenytoin, propranolol, and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin. However, there was one report of prolonged prothrombin time when buspirone was given to a patient also treated with warfarin, phenytoin, phenobarbital, digoxin, and Synthroid.

Carcinogenesis, Mutagenesis, Impairment of Fertility—No evidence of carcinogenic potential was observed in rats or mice; buspirone did not induce point mutations, nor was DNA damage observed; chromosomal aberrations or abnormalities did not occur.

Pregnancy: Teratogenic Effects—Pregnancy Category B. Should be used during pregnancy only if clearly needed.

Nursing Mothers—Administration to nursing women should be avoided if clinically possible.

Pediatric Use—The safety and effectiveness have not been determined in individuals below 18 years of age.

Use in the Elderly—No unusual, adverse, age-related phenomena have been identified in elderly patients receiving a total, modal daily dose of 15 mg.

Use in Patients with Impaired Hepatic or Renal Function—Since buspirone is metabolized by the liver and excreted by the kidneys, it is not recommended in severe hepatic or renal impairment.

Adverse Reactions (See also Precautions): ***Commonly Observed***—The more commonly observed untoward events, not seen at an equivalent incidence in placebo-treated patients, include dizziness, nausea, headache, nervousness, lightheadedness, and excitement.

Associated with Discontinuation of Treatment—The more common events causing discontinuation included: central nervous system disturbances (3.4%), primarily dizziness, insomnia, nervousness, drowsiness, lightheaded feeling; gastrointestinal disturbances (1.2%), primarily nausea; miscellaneous disturbances (1.1%), primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary.

Incidence in Controlled Clinical Trials—Adverse events reported by 1% or more of 477 patients who received buspirone in four-week, controlled trials. *Cardiovascular:* Tachycardia/palpitations 1%. *CNS:* Dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, lightheadedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2%. *EENT:* Blurred vision 2%. *Gastrointestinal:* Nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1%. *Musculoskeletal:* Musculoskeletal aches/pains 1%. *Neurological:* Numbness 2%, paresthesia 1%, incoordination 1%, tremor 1%. *Skin:* Skin rash 1%. *Miscellaneous:* Headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%.

Other Events Observed During the Entire Premarketing Evaluation—The relative frequency of all other undesirable events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under well-controlled, open, and uncontrolled conditions is defined as follows: Frequent are those occurring in at least 1/100 patients; infrequent are those occurring in 1/100 to 1/1000 patients, and rare are those occurring in less than 1/1000 patients. *Cardiovascular*—frequent: nonspecific chest pain; infrequent: syncope, hypotension, hypertension; rare: cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, bradycardia. *Central Nervous System*—frequent: dream disturbances; infrequent: depersonalization, dysphoria, noise intolerance, euphoria, akathisia, fearfulness, loss of interest, dissociative reaction, hallucinations, suicidal ideation, seizures; rare: feelings of claustrophobia, cold intolerance, stupor, slurred speech, psychosis. *EENT*—frequent: tinnitus, sore throat, nasal congestion; infrequent: redness and itching of the eyes, altered taste, altered smell, conjunctivitis; rare: inner ear abnormality, eye pain, photophobia, pressure on eyes. *Endocrine*—rare: galactorrhea, thyroid abnormality. *Gastrointestinal*—infrequent: flatulence, anorexia, increased appetite, salivation, irritable colon, rectal bleeding; rare: burning of the tongue. *Genitourinary*—infrequent: urinary frequency, urinary hesitancy, menstrual irregularity and spotting, dysuria; rare: amenorrhea, pelvic inflammatory disease, enuresis, nocturia. *Musculoskeletal*—infrequent: muscle cramps, muscle spasms, rigid/stiff muscles, arthralgias. *Neurological*—infrequent: involuntary movements, slowed reaction time; rare: muscle weakness. *Respiratory*—infrequent: hyperventilation, shortness of breath, chest congestion; rare: epistaxis. *Sexual Function*—infrequent: decreased or increased libido; rare: delayed ejaculation, impotence. *Skin*—infrequent: edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema, blisters; rare: acne, thinning of nails. *Clinical Laboratory*—infrequent: increases in hepatic aminotransferases (SGOT, SGPT); rare: eosinophilia, leukopenia, thrombocytopenia. *Miscellaneous*—infrequent: weight gain, fever, roaring sensation in the head, weight loss, malaise; rare: alcohol abuse, bleeding disturbance, loss of voice, hiccoughs.

Postintroduction Clinical Experience—Rare occurrences of allergic reactions, cogwheel rigidity, dystonic reactions, ecchymosis, emotional lability, tunnel vision, and urinary retention have been reported. Because of the uncontrolled nature of these spontaneous reports, a causal relationship to BuSpar has not been determined.

Drug Abuse and Dependence: ***Controlled Substance Class***—Not a controlled substance.

Physical and Psychological Dependence—Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. However, since it is difficult to predict from experiments the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (eg, development of tolerance, incrementation of dose, drug-seeking behavior).

Overdosage: ***Signs and Symptoms***—At doses approaching 375 mg/day the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. No deaths have been reported in humans either with deliberate or accidental overdosage.

Recommended Overdose Treatment—General symptomatic and supportive measures should be used along with immediate gastric lavage. No specific antidote is known and dialyzability of buspirone has not been determined.

For complete details, see Prescribing Information or consult your Mead Johnson Pharmaceuticals Representative.

U.S. Patent Nos. 3,717,634 and 4,182,763

MJL8-4270

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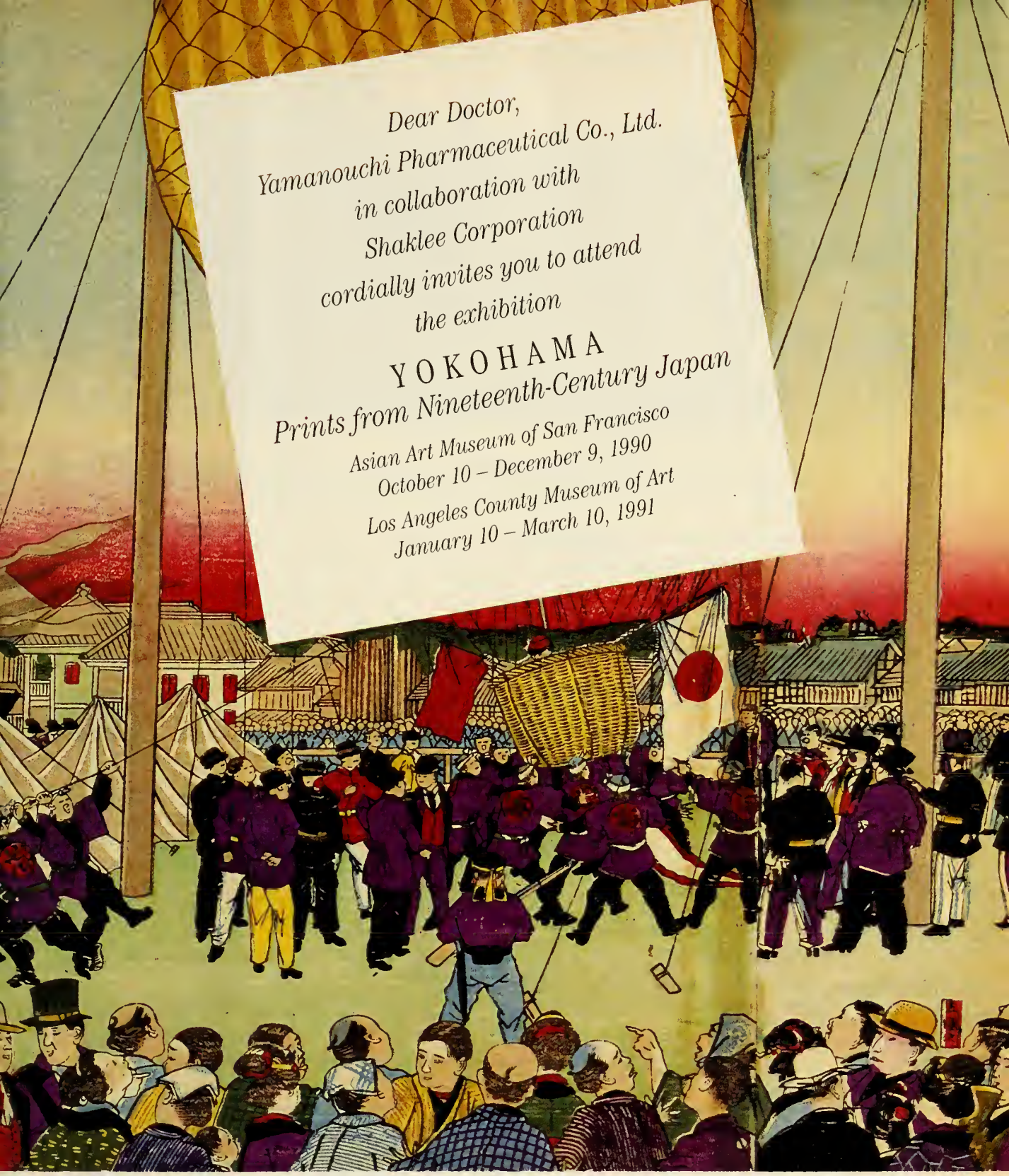

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421 **Human Obesity—Exploding the Myths**
Discussant: DAVID S. WEIGLE, MD

A discussion selected from the weekly Grand Rounds in the Department of Medicine, University of Washington School of Medicine, Seattle. Taken from a transcription, it was edited by Drs Paul G. Ramsey, Associate Professor of Medicine, and Philip J. Fialkow, Professor and Chair of the Department of Medicine.

429 **Editorial Comment: Is Obesity Due to a Heritable Difference in 'Set Point' for Adiposity?**
RUDOLPH L. LEIBEL, MD

From the Laboratory of Human Behavior and Metabolism, Rockefeller University, New York.

EPITOMES—IMPORTANT ADVANCES IN CLINICAL MEDICINE

Physical Medicine and Rehabilitation

Items of progress in physical medicine and rehabilitation. Each item, in the judgment of a panel of knowledgeable physicians, has recently became reasonably firmly established, both as to scientific fact and important clinical significance.

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D. NATHAN COPE, MD

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MURRAY E. BRANDSTATER, MBBS, PhD

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MERCEDES M. GARCIA, MD, and PAUL R. MERCER, MSW

From the Department of Psychiatry, University of California, Los Angeles, School of Medicine, and the Psychiatry Service, Veterans Administration Medical Center, Sepulveda, California. Dr Garcia is now in private practice in Los Angeles.

439 **Coexistence of Primary Biliary Cirrhosis and Sarcoidosis**
JONATHAN A. LEFF, MD; JOANNA B. READY, MD; CORINNA REPETTO, MD; JOHN S. GOFF, MD; and MARVIN I. SCHWARZ, MD

From the Division of Pulmonary Sciences, Webb-Waring Lung Institute, Division of Gastroenterology, Department of Medicine, University of Colorado Health Sciences Center, Denver.

(Continued on Page 368)

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Procardia XL®

(nifedipine) Extended Release

Tablets **30** mg, **60** mg and **90** mg **GITS**

The convenience of a once-a-day calcium channel blocker

Now available for your patients taking PROCARDIA® capsules (nifedipine)

The effectiveness you expect from nifedipine for a full 24 hours

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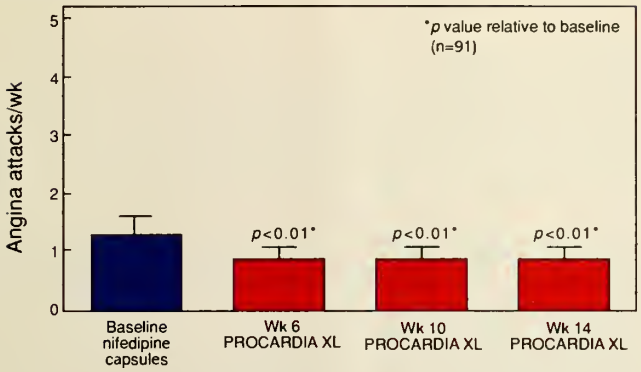
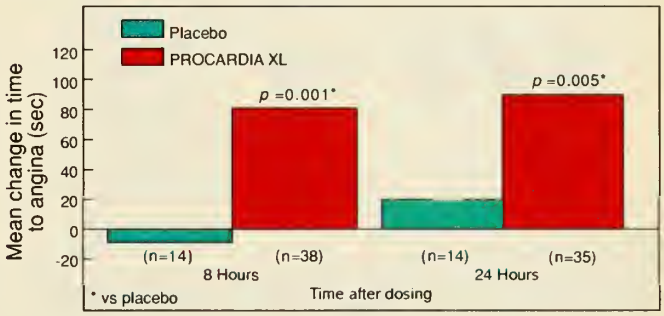


Fourteen-week, open-label, crossover trial to compare the efficacy and dose equivalence of nifedipine capsules (weeks 1 and 2) vs PROCARDIA XL (weeks 3-14) in 98 patients with chronic stable angina who had been on nifedipine capsules at least one month prior to the study. Patients were switched to the nearest equivalent daily dose over the dose range of 30-150 mg/day. Ninety-five patients were crossed over to receive PROCARDIA XL; 91 of these were evaluated for efficacy. The majority remained on beta blockers and/or nitrates throughout the study. (Reported by Vetrovec GW et al, *Am J Med*, 1987.[1])

Patients were of different races. (Data on file. Medical Department, Pfizer Labs, Pfizer Inc.[2])

TIME TO ANGINA[3]

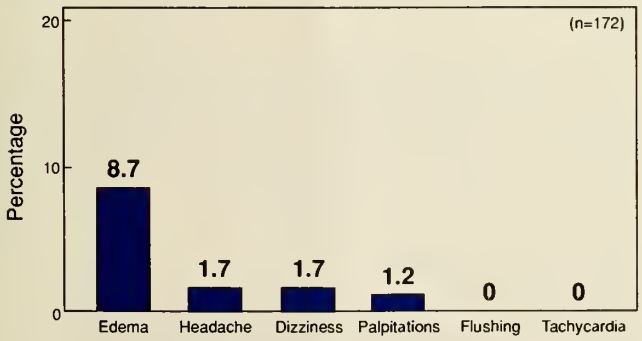


Double-blind, randomized, placebo-controlled, dose-response study. Patients were randomized to receive one of four treatments: PROCARDIA XL at a dose of 30, 60 or 90 mg qd plus beta blocker or placebo plus beta blocker. Exercise testing was performed at 8 and 24 hours post dose at the end of a 2-week baseline phase and a 2-week efficacy phase. (Reported by Bittar N, *Am J Cardiol*, 1989.[3])

Baseline time to angina was 290 sec. Baseline by dosage: 30 mg—269 sec; 60 mg—314 sec; 90 mg—254 sec. At the end of the efficacy phase, exercise-induced angina was present in 38 of 46 patients randomized to PROCARDIA XL and in 14 of 17 patients randomized to placebo. Patient population was predominantly white. (Data on file. Medical Department, Pfizer Labs, Pfizer Inc.[2])

...With a low incidence of vasodilatory side effects[2]

% INCIDENCE OF ADVERSE EXPERIENCES IN ANGINA PATIENTS[2]



Data obtained from multiple controlled trials of PROCARDIA XL (30-150 mg qd) in 172 patients with angina. (Data on file. Medical Department, Pfizer Labs, Pfizer Inc.[2])

- The most common side effects are peripheral edema, which is not associated with fluid retention, and headache

  In controlled studies of 776 patients with PROCARDIA XL, edema resulted in discontinuation of therapy in 2.7% of patients[2]

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Procardia XL®

(nifedipine) Extended Release

*Tablets **30** mg, **60** mg and **90** mg **GITS***

Easy mg-for-mg switch to convenient, once-daily dosing

- Over 90% of angina patients controlled on nifedipine capsules were easily switched to and controlled on PROCARDIA XL Extended Release Tablets at the nearest equivalent total daily dose; others needed dosage adjustment[2]

One 10-mg nifedipine capsule tid

One 30-mg PROCARDIA XL Extended Release Tablet qd

One 20-mg nifedipine capsule tid

One 60-mg PROCARDIA XL Extended Release Tablet qd

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Capsules	XL Tablets
30–40 mg/day in divided doses	→ **30 mg once a day**
50–70 mg/day in divided doses	→ **60 mg once a day**
80–100 mg/day in divided doses	→ **90 mg once a day**

- Subsequent dosage adjustments may be necessary and should be initiated as clinically warranted
- The total daily dose can be given with multiple tablets once a day, such as two 30-mg PROCARDIA XL Extended Release Tablets to equal 60 mg total daily dose
- Experience with doses >90 mg in patients with angina is limited; therefore, doses >90 mg should be used with caution and only when clinically warranted

References:

1. Vetrovec GW, Parket VE, Cole S, et al: Nifedipine gastrointestinal therapeutic system in stable angina pectoris. Results of a multicenter open-label crossover comparison with standard nifedipine. *Am J Med* 1987;83(suppl 6B):24-29
2. Data on file. Medical Department, Pfizer Labs. Pfizer Inc, New York
3. Bittar N. Usefulness of nifedipine for myocardial ischemia and the nifedipine gastrointestinal therapeutic system. *Am J Cardiol* 1989;64:31F-34F.

Brief Summary

PROCARDIA XL® (nifedipine) Extended Release Tablets For Oral Use

CONTRAINDICATIONS: Known hypersensitivity reaction to nifedipine

WARNINGS: Excessive Hypotension: Although in most angina patients the hypotensive effect of nifedipine is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving nifedipine together with a beta-blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of nifedipine and a beta blocker, but the possibility that it may occur with nifedipine alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In nifedipine-treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for nifedipine to be washed out of the body prior to surgery.

The following information should be taken into account in those patients who are being treated for hypertension as well as angina.

Increased Angina and/or Myocardial Infarction: Rarely, patients, particularly those who have severe obstructive coronary artery disease, have developed well documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting nifedipine or at the time of dosage increase. The mechanism of this effect is not established.

Beta Blocker Withdrawal: It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning nifedipine. Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of nifedipine treatment will not prevent this occurrence and on occasion has been reported to increase it.

Congestive Heart Failure: Rarely, patients usually receiving a beta blocker, have developed heart failure after beginning nifedipine. Patients with tight aortic stenosis may be at greater risk for such an event, as the unloading effect of nifedipine would be expected to be of less benefit to those patients, owing to their fixed impedance to flow across the aortic valve.

PRECAUTIONS: General—Hypotension: Because nifedipine decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of nifedipine is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See WARNINGS.)

Peripheral Edema: Mild to moderate peripheral edema occurs in a dose dependent manner with an incidence ranging from approximately 10% to about 30% at the highest dose studied (180 mg). It is a localized phenomenon thought to be associated with vasodilation of dependent arterioles and small blood vessels and not due to left ventricular dysfunction or generalized fluid retention. With patients whose angina or hypertension is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Other: As with any other non-deformable material, caution should be used when administering PROCARDIA XL in patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of PROCARDIA XL.

Laboratory Tests: Rare, usually transient, but occasionally significant elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted. The relationship to nifedipine therapy is uncertain in most cases, but probable in some. These laboratory abnormalities have rarely been associated with clinical symptoms; however, cholestasis with or without jaundice has been reported. A small (5.4%) increase in mean alkaline phosphatase was noted in patients treated with PROCARDIA XL. This was an isolated finding not associated with clinical symptoms and it rarely resulted in values which fell outside the normal range. Rare instances of allergic hepatitis have been reported. In controlled studies, PROCARDIA XL did not adversely affect serum uric acid, glucose, or cholesterol. Serum potassium was unchanged in patients receiving PROCARDIA XL in the absence of concomitant diuretic therapy, and slightly decreased in patients receiving concomitant diuretics.

Nifedipine, like other calcium channel blockers, decreases platelet aggregation *in vitro*. Limited clinical studies have demonstrated a moderate but statistically significant decrease in platelet aggregation and increase in bleeding time in some nifedipine patients. This is thought to be a function of inhibition of calcium transport across the platelet membrane. No clinical significance for these findings has been demonstrated.

Positive direct Coombs test with/without hemolytic anemia has been reported but a causal relationship between nifedipine administration and positivity of this laboratory test, including hemolysis, could not be determined.

Although nifedipine has been used safely in patients with renal dysfunction and has been reported to exert a beneficial effect in certain cases, rare reversible elevations in BUN and serum creatinine have been reported in patients with pre-existing chronic renal insufficiency. The relationship to nifedipine therapy is uncertain in most cases but probable in some.

Drug Interactions—Beta-adrenergic blocking agents: (See WARNINGS) Experience in over 1400 patients with Procardia® capsules in a noncomparative clinical trial has shown that concomitant administration of nifedipine and beta-blocking agents is usually well tolerated but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension, or exacerbation of angina.

Long Acting Nitrates: Nifedipine may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Digitalis: Administration of nifedipine with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing nifedipine to avoid possible over- or under-digitalization.

Coumarin Anticoagulants: There have been rare reports of increased prothrombin time in patients taking coumarin anticoagulants to whom nifedipine was administered. However, the relationship to nifedipine therapy is uncertain.

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak nifedipine plasma levels (80%) and area-under-the-curve (74%), after a one week course of cimetidine at 1000 mg per day and nifedipine at 40 mg per day. Ranitidine produced smaller, non-significant increases. The effect may be mediated by the known inhibition of cimetidine on hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of nifedipine. If nifedipine therapy is initiated in a patient currently receiving cimetidine, cautious titration is advised.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Nifedipine was administered orally to rats, for two years and was not shown to be carcinogenic. When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose. *In vivo* mutagenicity studies were negative.

Pregnancy: Pregnancy Category C. Nifedipine has been shown to be teratogenic in rats when given in doses 30 times the maximum recommended human dose. Nifedipine was embryotoxic (increased fetal resorptions, decreased fetal weight, increased stunted forms, increased fetal deaths, decreased neonatal survival) in rats, mice, and rabbits at doses of from 3 to 10 times the maximum recommended human dose. In pregnant monkeys, doses 2/3 and twice the maximum recommended human dose resulted in small placentas and underdeveloped chorionic villi. In rats, doses three times maximum human dose and higher caused prolongation of pregnancy. There are no adequate and well controlled studies in pregnant women. PRDCARDIA XL® (nifedipine) Extended Release Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

ADVERSE EXPERIENCES: Over 1000 patients from both controlled and open trials with PROCAROIA XL Extended Release Tablets in hypertension and angina were included in the evaluation of adverse experiences. All side effects reported during PROCARDIA XL Extended Release Tablet therapy were tabulated independent of their causal relation to medication. The most common side effect reported with PRDCARDIA XL was edema which was dose related and ranged in frequency from approximately 10% to about 30% at the highest dose studied (180 mg). Other common adverse experiences reported in placebo-controlled trials include: headache (15.8%, compared to 9.8% placebo incidence), fatigue (5.9%, compared to 4.1% placebo incidence), dizziness (4.1%, compared to 4.5% placebo incidence), constipation (3.3%, compared to 2.3% placebo incidence), and nausea (3.3%, compared to 1.9% placebo incidence). Of these, only edema and headache were more common in PROCARDIA XL patients than placebo patients.

The following adverse reactions occurred with an incidence of less than 3.0%. With the exception of leg cramps, the incidence of these side effects was similar to that of placebo alone: *body as a whole/systemic*: asthenia, flushing, pain; *cardiovascular*: palpitations; *central nervous system*: insomnia, nervousness, paresthesia, somnolence; *dermatologic*: pruritus, rash; *gastrointestinal*: abdominal pain, diarrhea, dry mouth, dyspepsia, flatulence; *musculoskeletal*: arthralgia, leg cramps; *respiratory*: chest pain (nonspecific), dyspnea; *urogenital*: impotence, polyuria.

Other adverse reactions were reported sporadically with an incidence of 1.0% or less. These include: *body as a whole/systemic*: face edema, fever, hot flashes, malaise, periorbital edema, rigors; *cardiovascular*: arrhythmia, hypotension, increased angina, tachycardia, syncope; *central nervous system*: anxiety, ataxia, decreased libido, depression, hypertonia, hypoesthesia, migraine, paronirria, tremor, vertigo; *dermatologic*: alopecia, increased sweating, urticana, purpura; *gastrointestinal*: eructation, gastroesophageal reflux, gum hyperplasia, melena, vomiting, weight increase; *musculoskeletal*: back pain, gout, myalgias; *respiratory*: coughing, epistaxis, upper respiratory tract infection, respiratory disorder, sinusitis; *special senses*: abnormal lacrimation, abnormal vision, taste perversion, tinnitus; *urogenital/reproductive*: breast pain, dysuria, hematuria, nocturia.

Adverse experiences which occurred in less than 1 in 1000 patients cannot be distinguished from concurrent disease states or medications.

The following adverse experiences, reported in less than 1% of patients, occurred under conditions (e.g., open trials, marketing experience) where a causal relationship is uncertain: gastrointestinal irritation, gastrointestinal bleeding.

In multiple-dose U.S. and foreign controlled studies with nifedipine capsules in which adverse reactions were reported spontaneously, adverse effects were frequent but generally not serious and rarely required discontinuation of therapy or dosage adjustment. Most were expected consequences of the vasodilator effects of Procardia. Adverse experiences reported in placebo-controlled trials include: dizziness, lightheadedness, and giddiness (27%, compared to 15% placebo incidence); flushing, heat sensation (25%, compared to 8% placebo incidence); headache (23%, compared to 20% placebo incidence); weakness (12%, compared to 10% placebo incidence); nausea, heartburn (11%, compared to 8% placebo incidence), muscle cramps, tremor (8%, compared to 3% placebo incidence); peripheral edema (7%, compared to 1% placebo incidence), nervousness, mood changes (7%, compared to 4% placebo incidence); palpitation (7%, compared to 5% placebo incidence); dyspnea, cough, and wheezing (6%, compared to 3% placebo incidence); and nasal congestion, sore throat (6%, compared to 8% placebo incidence).

There is also a large uncontrolled experience in over 2100 patients in the United States. Most of the patients had vasospastic or resistant angina pectoris, and about half had concomitant treatment with beta-adrenergic blocking agents. The relatively common adverse events were similar in nature to those seen with PRDCARDIA XL.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

In a subgroup of over 1000 patients receiving Procardia with concomitant beta blocker therapy, the pattern and incidence of adverse experiences was not different from that of the entire group of Procardia treated patients (See PRECAUTIDNS.)

In a subgroup of approximately 250 patients with a diagnosis of congestive heart failure as well as angina, dizziness or lightheadedness, peripheral edema, headache or flushing each occurred in one in eight patients. Hypotension occurred in about one in 20 patients. Syncope occurred in approximately one patient in 250. Myocardial infarction or symptoms of congestive heart failure each occurred in about one patient in 15. Atrial or ventricular dysrhythmias each occurred in about one patient in 150.

In post-marketing experience, there have been rare reports of exfoliative dermatitis caused by nifedipine.

More detailed professional information available on request

Revised July 1990

Pfizer Labs

THE WESTERN JOURNAL OF MEDICINE

INFORMATION FOR AUTHORS

Submitting Manuscripts

Manuscripts for consideration should be sent to the editor, Linda Hawes Clever, MD, PO Box 7602, San Francisco, CA 94120-7602. The transmittal letter should designate one person as correspondent and include complete address, with ZIP code and telephone number.

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Authors are urged to seek clarity and succinctness in all manuscripts regardless of subject matter or format and to give close attention to syntax, grammar, and spelling.

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The original manuscript and *two* copies should be submitted on heavy bond paper (8½ by 11 inches, *not* erasable), typed *double-spaced throughout* (including legends, tables, and references) on one side of the paper, with 1½-inch margins. Articles should not exceed 3,000 words (less than 15 text pages typed double-spaced). Under exceptional circumstances only will articles longer than 4,000 words be published. Pages should be numbered consecutively, beginning with the title page. Manuscripts produced with a dot-matrix printer are ordinarily not acceptable.

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Tables and Figures

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Three sets of clear, unmounted black and white glossy prints of figures should be submitted (preferably 5 by 7 inches, but no larger than 8½ by 11 inches). For line drawings, original artwork or glossy prints are acceptable. Illustrations should be numbered consecutively in Arabic numerals and the position indicated in the text. Figure number, first author's name and top of the photo should be shown on the reverse side of each illustration. Recognizable photographs of patients are to be masked and written permission for publication obtained from the patients.

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Note handling of multiple authorship. If more than three authors are listed as contributors, use "et al" to designate those names after the first three. Also note capitalization, punctuation, use of inclusive page numbers, and year of publication. Separate the subtitle from the title by either a dash or a colon. Use colon *only* if it appears in the original citation.

1. Jones JS, Anderson HW, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978; 292:444-456
2. Graybill JR, Alford RH, Smith RG, et al: Cell-mediated immunity in cryptococcosis: A brief review. Cell Immunol 1978; 7:76-79

Books

Note handling of "edition," "editor(s)," and "volume," as well as appropriate sequence of reference information and capitalization of chapters and titles.

3. Berne EJ, Smith TL: Role playing in therapy, chap 2, Principles of Group Therapy. New York, Oxford University Press, 1966, pp 35-51 *(author of chapter same as author of book)*
4. Munsung JM: The role of drugs, chap 2, *In* Brest AN, Mayer JH (Eds): Hypertension—Vol 2, Therapy, 2nd Ed. Springfield, Ill, Charles C Thomas, 1961, pp 456-479 *(author of chapter different from authors of book)*

Pamphlets, Monographs, or Books With No Given Author

5. AMA Department of Drugs: AMA Drug Evaluation, 3rd Ed. Littleton, Mass, Publishing Sciences Group, 1977 *(corporate author)*
6. Compilation of Standard Definitions, 3rd Ed. Philadelphia, American Society for Testing and Materials, 1976 *(no given author; give name and place of publisher)*

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Acknowledgments

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Brochures and registration forms are available from the contact person or organization sponsoring the program.

October 19-20—**Common Clinical Problems in the Elderly and Nursing Home Care.** Arizona Geriatrics Society at Arizona Golf Resort and Conference Center, Mesa. Fri-Sat. Contact: Marian Richardson, (602) 974-4212.

October 19-21—**The 1990 Joint Annual Meeting of the Southwestern and Texas Dermatological Societies.** The Ritz-Carlton, Phoenix. Fri-Sun. Contact: (800) 241-3333.

October 25—**Pediatric Emergencies: A Practical Approach.** University of Arizona at Hotel Park Tucson, Tucson. Contact: Lynne Mascarella, (602) 626-7832.

October 27—**6th Bi-Annual Otolaryngology-Head and Neck Surgery Seminar.** Mayo Clinic-Scottsdale. Sat. Contact: Trish Gean, (602) 391-8300.

November 8-10—**Third Annual Spine Workshop.** Barrow Neurological Institute at Marriott's Mountain Shadows Resort, Scottsdale. Thurs-Sat. Contact: Toby Jardine, RN, MA, (602) 285-3178 or 1-800-Barrow-1.

November 15-18—**Psychiatric Medicine in the '90s: The Emergence of Consultation/Liaison Psychiatry.** Academy of Psychosomatic Medicine, 37th Annual Meeting, at The Pointe—Squaw Peak, Phoenix. Thurs-Sun. Contact: (312) 784-2025.

November 16-17—**Techniques in Gynecologic Surgery.** Mayo Clinic-Scottsdale at Hyatt Regency Scottsdale at Gainey Ranch, Scottsdale. Fri-Sat. Contact: Jodi Lee Smith, (602) 391-7072.

November 17-18—**Obstetrical Pathology: POC, Placental and Perinatal Disorders.** Arizona Society of Pathologists at the Clarion Hotel, Scottsdale. Sat-Sun. Contact: Beverly Reichter, (602) 246-8901.

November 18-21—**7th Annual State of the Art in Total Joint Replacement.** Harrington Arthritis Research Center at Scottsdale Princess Resort, Scottsdale. Sun-Wed. Contact: Nancy Neroni, (602) 254-0377.

January 19—**Current Topics in Anesthesia.** Mayo Clinic-Scottsdale. Sat. Contact: Trish Gean, (602) 391-8300.

February 15-17—**Anesthesia for the 90s: 17th Annual Scientific Meeting.** Arizona Society of Anesthesiologists at Wyndham Paradise Valley Resort, Paradise Valley. Fri-Sun. Contact: Beverly Reichter, (602) 246-8901.

February 21-23—**17th Annual Frontiers in Ophthalmology.** St Luke's Medical Center at Red Lion's La Posada Resort, Scottsdale. Thurs-Sat. Contact: Christine Campbell, (602) 820-7027.

February 28-March 2—**13th Annual Postgraduate Course: Advances in Obstetrics and Gynecology.** Maricopa Medical Center and Phoenix OB/GYN Society at the Scottsdale Hilton Hotel, Scottsdale. Thurs-Sat. Contact: (602) 266-6321.

March 16-20—**Fifth Annual Magnetic Resonance Imaging Conference.** Barrow Neurological Institute at Marriott's Camelback Inn, Scottsdale. Sat-Wed. Contact: Kevin King, RT, (602) 285-3956.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Jodi Lee Smith, Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 391-8300.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6707.

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This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 541-0900. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

October 28-November 2—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Westin Maui Hotel, Kaanapali Beach, Hawaii. Sun-Fri. 20 hrs. $345. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

November 16-18—**Anesthesiology Update: 1990.** UCD at Monterey Plaza. Fri-Sun. 14 hrs. $350. Contact: UCD.

January 20-26—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Sheraton Hotel, Poipu Beach, Kauai. Sun-Sat. 20 hrs. $345. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7186.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

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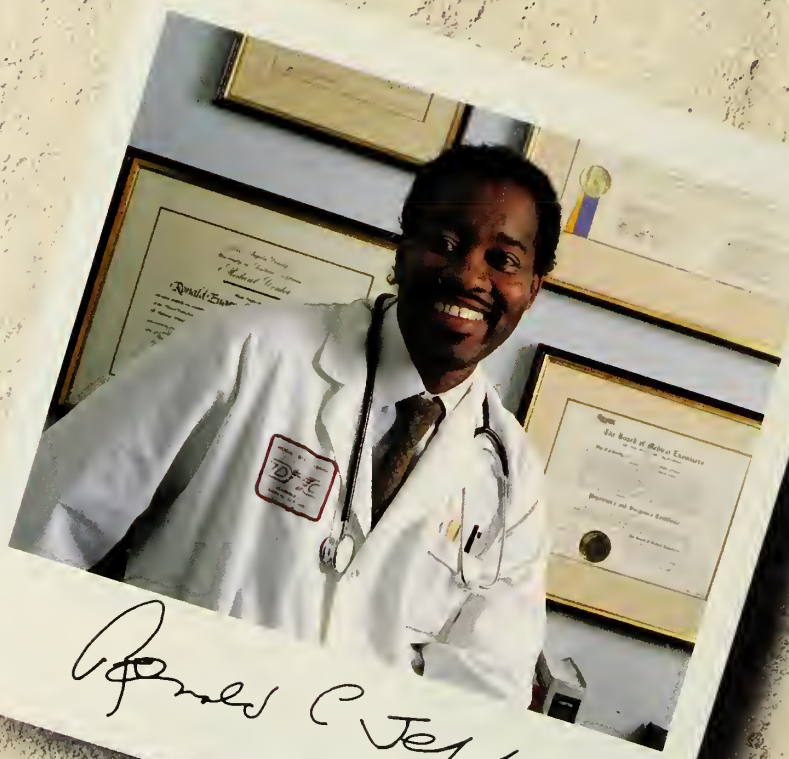

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Applies to California residents only.

(Continued from Page 370)

January 25-27—**29th Clinical Conference in Pediatric Anesthesiology.** Children's Hospital Pediatric Anesthesiology Foundation at Stouffer Concourse Hotel. Fri-Sun. 15 hrs. Contact: Katherine Barky, MD, PO Box 54700, Los Angeles 90054.

February 3-8—**Clinical Update in Anesthesiology.** Biennial Western Conference on Anesthesiology at Stouffer's Wailea Beach Resort, Maui, Hawaii. Sun-Fri. Contact: Murray Atnikov, MD, c/o PO Box F110-63, Blaine, WA 98230. (604) 874-5291.

CARDIOLOGY

October 19-20—**Series I—Coronary Heart Disease Update.** Medical Education Resources at Grand Hyatt Union Square, San Francisco. Fri-Sat. 11 hrs. $295. Contact: MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80123. (800) 421-3756.

October 26-27—**Series II—Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Las Vegas Hilton. Fri-Sat. 12 hrs. $275. Contact: MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80123. (800) 421-3756.

November 3—**Myocardial Infarction: Contemporary Management.** UCD at Capitol Plaza Holiday Inn, Sacramento. Sat. 7 hrs. $120. Contact: UCD.

December 1—**8th Annual Reider Laser Center: International Pulmonary Symposium on Brachytherapy and Argon and ND: YAG Lasers with ND: YAG Laser Workshop.** Memorial/UCI Center for Health Education at Long Beach. Sat. Contact: UCI.

January 24-26—**Cardiology '91.** Cardiovascular Institute at La Jolla Marriott. Thurs-Sat. Contact: Janice Turner, PO Box 2586, La Jolla 92038. (619) 459-1564.

DERMATOLOGY

October 20-21—**The Skin from A to Z.** UCSF at Laurel Heights Campus, San Francisco. Sat-Sun. 10 hrs. $205. Contact: UCSF.

January 17-19—**Workshop in Dermatopathology.** Scripps Clinic and Research Foundation at Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Sat. 20 hrs. $400. Contact: Susan J Buntjer, 400S, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

January 24-26—**Cutaneous Malignancies: 1991 Skin Cancer Update.** Scripps Clinic and Research Foundation at Hyatt Regency, La Jolla. Thurs-Sat. 12 hrs. $350. Contact: Susan Buntjer, 400S, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

EMERGENCY MEDICINE

October 22-26—**Postgraduate Institute for Primary Care and Emergency Physicians Symposium I: Cardiology, Pulmonary, Neurology.** Mon-Fri. 32 hrs. $450. Contact: UCSD.

October 29-November 3—**Topics in Emergency Medicine.** UCSF at Holiday Inn Union Square, SF. Mon-Sat. 32 hrs. $460. Contact: UCSF.

November 12-16—**Emergency Medicine Symposium III: Pediatrics, OB/GYN, Legal Aspects, Dermatology.** UCSD at Hyatt Regency, La Jolla. Mon-Fri. 32 hrs. $450. Contact: UCSD.

December 10-14—**Emergency Medicine Symposium II: Trauma and Surgery.** UCSD at La Jolla Marriott. Mon-Fri. 32 hrs. $485. Contact: UCSD.

January 14-18—**Emergency Medicine Symposium I: Cardiology, Pulmonary, Neurology.** UCSD at Hyatt Regency, La Jolla. 32 hrs. $485. Contact: UCSD.

February 24-March 1—**Annual Emergency Medicine.** UCD at Hyatt Lake Tahoe, Incline Village, NV. Sun-Fri. Contact: UCD.

March 18-22—**Symposium II: Trauma and Surgery.** UCSD at La Jolla Marriott. Mon-Fri. 32 hrs. $485. Contact: UCSD.

FAMILY PRACTICE/PRIMARY CARE

October 31-November 4—**The Office Practice of Primary Care Medicine: Common Problems and Practical Solutions.** Sharp Memorial Hospital at Le Meridien San Diego, Coronado. Wed-Sun. 23-27 hrs. $360. Contact: Sharp Memorial Hospital, CME Dept, (619) 541-4530.

November 10-11—**Desert Medical Series II: Family Crisis in Family Medicine—Dealing with the Dilemmas of Aging.** Annenberg Center for Health Sciences at Eisenhower. Sat-Sun. Contact: ACHS, 39000 Bob Hope Dr, Rancho Mirage 92270. (800) 321-3690.

January 26-February 2—**Vascular Update 1991.** University of Washington School of Medicine at Westin Hotel, Kauai, Hawaii. One week. Contact: U/W School of Medicine, Div of CME, SC-50, Seattle 98195. (206) 543-1050.

January 31-February 2—**Adolescent Medicine for the Practitioner.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Sat. Contact: Laurie Jones, Box 400S, Scripps Clinic, 10666 N Torrey Pines Road, La Jolla 92037. (619) 554-9592.

February 11-15—**Family Practice Refresher Course.** UCI at Westin South Coast Plaza, Costa Mesa. Mon-Fri. Contact: UCI.

February 20-23—**The Practicing Physician's Approach to the Difficult Headache Patient.** Scripps Clinic and Research Foundation and Diamond Headache Clinic at Wyndham Hotel, Palm Springs. Wed-Sat. 15 hrs. Contact: Idell Applebaum, 5252 N Western Ave, Chicago, IL 60625. (312) 878-5558.

INTERNAL MEDICINE

October 18-20—**Breast Cancer Seminar.** Memorial/UCI Center for Health Education at Stouffer Hotel, Palm Springs. Thurs-Sat. Contact: UCI.

October 22-24—**14th Annual Cancer Symposium.** Scripps Memorial Hospital at Sheraton Harbor Island Hotel, San Diego. Mon-Wed. 20 hrs. $390. Contact: Meeting Management, 5665 Oberlin Dr, Ste 110, San Diego 92121. (619) 453-6222.

October 20—**Lipids Conference.** UCD at Sheraton Sunrise, Sacramento. Sat. Contact: UCD.

November 9-10—**Metabolic Control of Diabetes.** Memorial/UCI Center for Health Education at Westin South Coast Plaza, Costa Mesa. Fri-Sat. Contact: UCI.

November 30-December 1—**Northern California Internal Medicine Update.** UCD at Hilton Inn. Fri-Sat. Contact: UCD.

December 6-9—**Fall Symposium on Back Pain.** American Back Society at San Francisco Marriott Hotel. Thurs-Sun. 18 hrs. Contact: Aubrey Swartz, MD, ABS, 2647 E 14th St, Ste 401, Oakland 94601. (415) 536-9929.

January 31-February 2—**Advanced Nephrology: Nephrology for the Consultant.** UCSD at Sheraton Grand Hotel, San Diego. Thurs-Sat. 17 hrs. $350. Contact: Meeting Management, 5665 Oberlin Dr, Ste 110, San Diego 92121. (619) 453-6222.

February 1-3—**8th Annual Reider Laser Symposium-Urology.** Memorial/UCI Center for Health Education at Palm Springs. Fri-Sun. Contact: UCI.

February 15-17—**24th Annual Recent Advances in Neurology.** UCSF at San Francisco. Fri-Sun. 15 hrs. Contact: UCSF.

February 18-20—**Clinical Hematology and Oncology: 1991.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Wed. 18 hrs. $385. Contact: Susan Buntjer, 400S, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

March 6-7—**Advances in Endocrinology and Metabolism.** UCSF at Sheraton Palace Hotel, San Francisco. Wed-Thurs. 14 hrs. $295. Contact: UCSF.

March 8-9—**Diabetes Update.** UCSF at Sheraton Palace Hotel, San Francisco. Fri-Sat. 10 hrs. $245. Contact: UCSF.

OB/GYN

November 8-11—**Current Issues in Perinatal Medicine.** Memorial/UCI Center for Health Education at Marriott's Rancho Las Palmas Resort, Palm Springs. Thurs-Sun. Contact: UCI.

November 11—**Review Course in Gynecologic Pathology.** USC at Pasadena Hilton Hotel. Sun. 6 hrs. $140. Contact: USC.

November 11-17—**13th Annual Review Course in Clinical OB/GYN and/or Gynecological Histopathology.** Memorial/UCI Center for Health Education at Westin South Coast Plaza, Costa Mesa. 1 week. Contact: UCI.

November 12-16—**23rd Review Course in Obstetrics and Gynecology.** USC at Pasadena Hilton Hotel. Mon-Fri. $640. 38 hrs. Contact: USC.

November 29-December 1—**Nebraska OB/GYN Society Meeting.** Nebraska OB/GYN at Las Vegas, Nevada. Thurs-Sat. Contact: University of Nebraska Medical Center, 42nd and Dewey Ave, Omaha, NE 68105-1065. (402) 559-4152.

February 1-3—**8th Annual Reider Laser Symposium-Gynecology.** Memorial/UCI Center for Health Education at Palm Springs. Fri-Sun. Contact: UCI.

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(Continued from Page 373)

February 14-17—**46th Annual Postgraduate Assembly.** OB-GYN Assembly of Southern California at Beverly Hilton Hotel, Beverly Hills. Thurs-Sun. 28 hrs. Contact: OB-GYN Assembly, 5820 Wilshire Blvd, No. 500, Los Angeles 90036. (213) 937-5514.

OCCUPATIONAL AND ENVIRONMENTAL MEDICINE

October 8-19—**Occupational and Environmental Medicine: Session II.** UCSF at Cathedral Hill Hotel, San Francisco. 1½ weeks. 80 hrs. $1,200. Contact: UCSF.

October 15-19—**Current Topics in Occupational Medicine.** UCSF at Cathedral Hill Hotel, San Francisco. Mon-Fri. 40 hrs. $600. Contact: UCSF.

November 8-11—**Western Occupational Conference.** Western Occupational Medical Association at Los Angeles Airport Hilton. Thurs-Sun. 23 hrs. Contact: Carol Parlette, MPH, (415) 764-4803.

January 28-February 8—**Occupational and Environmental Medicine: Session I.** UCSF at Cathedral Hill Hotel, San Francisco. 1½ wks. 80 hrs. $1,200. Contact: UCSF.

February 11-15—**Occupational and Environmental Medicine: Session III.** UCSF at Cathedral Hill Hotel, San Francisco. Mon-Fri. 40 hrs. $600. Contact: UCSF.

OPHTHALMOLOGY

November 30-December 2—**American Academy of Ophthalmology Regional Update Course.** American Academy of Ophthalmology at Los Angeles. Fri-Sun. Contact: Gary Holland, (213) 825-9508.

December 13-14—**New Ideas on Common Retinal Disorders.** UCSF at Grand Hyatt Union Square, San Francisco. Thurs-Fri. 12 hrs. $300. Contact: UCSF.

January 13-16—**Contact Lens Association of Ophthalmologists 1991 Annual Meeting.** CLAO at Caesars Palace, Las Vegas, Nevada. Sun-Wed. Contact: CLAO, 523 Decatur St, Ste One, New Orleans, LA 70130-1027. (504) 581-4000.

February 3-7—**10th Annual Squaw Valley Retina Symposium.** Alta-California Ophthalmological Society at Squaw Valley Inn, Olympic Valley. Sun-Thurs. 16 hrs. Contact: Mercy General Hospital, Community Relations, 4001 "J" St, Sacramento 95819. (916) 454-4410.

February 8-10—**60th Midwinter Clinical Conference.** Research Study Club of Los Angeles at Moseley/Salvatori Conference Center, Los Angeles. Fri-Sun. Contact: Research Study Club, PO Box 1216, Murrieta 92362. (714) 677-4482.

ORTHOPEDICS

December 6—**Common Musculoskeletal Problems—Foot and Ankle.** VA Medical Center Sepulveda. Thurs. 5 hrs. Contact: Arun Mehta, MD, Rehabilitation Medicine Service (117), VAMC Sepulveda 91343. (818) 895-9344.

OTOLARYNGOLOGY

November 8-10—**Otolaryngology Update: 1990.** UCSF at Union Square Holiday Inn, San Francisco. Thurs-Sat. 18 hrs. $375. Contact: UCSF.

February 8-10—**60th Midwinter Clinical Conference.** Research Study Club of Los Angeles at Moseley/Salvatori Conference Center. Fri-Sun. Contact: Research Study Club, PO Box 1216, Murrieta 92362. (714) 677-4482.

January 18-20—**Triological Society Western Section.** Triological Society at Santa Barbara Biltmore Hotel. Fri-Sun. Contact: David Hilding, MD, Ste 1, Hospital Dr, Price, UT 84501. (801) 637-4327.

PATHOLOGY

October 19—**Fine Needle Aspiration Tutorials.** UCSF. Fri. 7 hrs. Contact: UCSF.

October 20—**30th Annual Scientific Symposium on Kidney Disease.** National Kidney Foundation of Southern California at Wyndham Palm Springs. Sat. Contact: Sylvie Tarro, 5777 W Century Blvd, Ste 395, Los Angeles 90045. (213) 641-8152.

November 2-3—**Update on Thyroid Disease—1990.** UCSF at Hyatt Regency Embarcadero, San Francisco. Fri-Sat. 12 hrs. $150. Contact: UCSF.

November 10—**Infectious Diseases in Critical Care.** UCD at Hilton Inn, Sacramento. Sat. 6 hrs. $80. Contact: UCD.

February 13-15—**Clinical Laboratory Molecular Analysis.** Scripps Clinic and Research Foundation at Hyatt Regency Hotel, La Jolla. Wed-Fri. 21 hrs. $375. Contact: Laurie Jones, Box 400S, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-9592.

PEDIATRICS

October 18-21—**47th Annual Brennemann Memorial Lectures.** Los Angeles Pediatric Society at San Diego Marriott-La Jolla Hotel, La Jolla. Thurs-Sun. 15 hrs. $325. Contact: LAPS, (213) 757-1198.

November 9-11—**Infectious Diseases in Children.** Children's Hospital Oakland at Monterey Plaza Hotel on Cannery Row. Fri-Sun. 12 hrs. $280. Contact: Kim Leadon, 747 52nd St, Oakland 94609. (415) 428-3021.

December 1—**8th Annual Binational Pediatric Conference.** Children's Hospital San Diego at Mercy Hospital Education Center, San Diego. Sat. 5 hrs. Contact: CME Dept, Children's Hospital, (619) 576-4072.

December 8-9-**Stabilization and Management of the Critically Ill Child.** UCSF at Hyatt Regency Hotel, San Francisco. Sat-Sun. 9 hrs. Contact: UCSF.

January 23-26—**Health Science Response to Child Maltreatment 1991.** Children's Hospital San Diego at U S Grant Hotel, San Diego. Wed-Sat. 22 hrs. Contact: Children's Hospital, (619) 576-5814.

February 8-10—**Current Concepts in Pediatric Medicine 1991.** Children's Hospital San Diego at Hyatt Islandia Hotel, San Diego. Fri-Sun. 18 hrs. Contact: CME Dept. Children's Hospital, (619) 576-4072.

PSYCHIATRY

October 19-21—**Creating an Integrated Psychiatry: Challenge of the 90's.** California Psychiatric Association at Claremont Hotel, Berkeley. Fri-Sun. 11 hrs. Contact: Barbara Gard, 1100 N St, Ste 2-E, Sacramento 95814. (916) 442-5196.

October 26-27—**The Aftermath of Suicide: Counseling Survivors.** UCSF on Campus. Fri-Sat. $190. Contact: UCSF.

November 9-11—**36th Annual Group Therapy Symposium.** UCSF at Sir Francis Drake Hotel, San Francisco. Fri-Sun. 21 hrs. $195. Contact: UCSF.

November 12-16—**Introduction to Medical Hypnosis.** UCSD at Inn at Del Mar. Mon-Fri. Contact: UCSD.

January 27-February 1—**17th Annual Midwinter Program for Psychiatrists: Special Focus on Psychic Trauma.** UCD at Hyatt Regency, Incline Village, Nevada. Sun-Fri. 25 hrs. $395. Contact: UCD.

RADIOLOGY

October 20-21—**Advanced Imaging of the Musculoskeletal System.** UCSD at Hotel del Coronado, San Diego. Sat-Sun. 12 hrs. $125. Contact: UCSD.

October 22-26—**15th Annual San Diego Postgraduate Course.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 27 hrs. $300. Contact: UCSD.

October 26-28—**10th Annual Interventional Radiology.** UCSD at Hotel del Coronado, San Diego. Fri-Sun. 18 hrs. $350. Contact: UCSD.

November 9-11—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton Resort Hotel, Laguna Niguel. Fri-Sun. 20 hrs. $400. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

December 7-9—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton Resort Hotel, Laguna Niguel. Fri-Sun. 18 hrs. $400. Contact: UCSD.

January 19-21—**Advanced Seminars in Diagnostic Imaging.** UCSF at Ritz-Carlton Resort Hotel, Laguna Niguel. Sat-Mon. 20 hrs. $400. Contact: UCSF.

February 1-3—**43rd Midwinter Radiological Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Fri-Sun. 17 hrs. $395. Contact: LARS, PO Box 91215, Los Angeles 90009-1215. (213) 827-9078.

February 4-5—**Angio-Interventional Radiology.** UCSD at Le Meridien Hotel, San Diego. Mon-Tues. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

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"Recent research has delineated early, more subtle changes in lung and immune functions. These alterations directly predispose smokers to respiratory tract infection."

Am Fam Phys 1987;36:133-140

Ceclor® Pulvules® 250 mg
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For respiratory tract infections due to susceptible strains of indicated organisms

Brief Summary.
Consult the package literature for prescribing information.
Indication: Lower respiratory infections, including pneumonia, caused by *Streptococcus pneumoniae, Haemophilus influenzae,* and *Streptococcus pyogenes* (group A β-hemolytic streptococci).
Contraindication: Known allergy to cephalosporins.
Warnings: CECLOR SHOULD BE ADMINISTERED CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. PENICILLINS AND CEPHALOSPORINS SHOW PARTIAL CROSS-ALLERGENICITY. POSSIBLE REACTIONS INCLUDE ANAPHYLAXIS.

Administer cautiously to allergic patients.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics. It must be considered in differential diagnosis of antibiotic-associated diarrhea. Colon flora is altered by broad-spectrum antibiotic treatment, possibly resulting in antibiotic-associated colitis.

Precautions:
• Discontinue Ceclor in the event of allergic reactions to it.
• Prolonged use may result in overgrowth of nonsusceptible organisms.
• Positive direct Coombs' tests have been reported during treatment with cephalosporins.
• Ceclor should be administered with caution in the presence of markedly impaired renal function. Although dosage adjustments in moderate to severe renal impairment are usually not required, careful clinical observation and laboratory studies should be made.
• Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.
• Safety and effectiveness have not been determined in pregnancy, lactation, and infants less than one month old. Ceclor penetrates mother's milk. Exercise caution in prescribing for these patients.

Adverse Reactions: (percentage of patients)

Therapy-related adverse reactions are uncommon. Those reported include:
• Hypersensitivity reactions have been reported in about 1.5% of patients and include morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs' tests each occur in less than 1 in 200 patients. Cases of **serum-sickness-like** reactions have been reported with the use of Ceclor. These are characterized by findings of erythema multiforme, rashes, and other skin manifestations accompanied by arthritis/arthralgia, with or without fever, and differ from classic serum sickness in that there is infrequently associated lymphadenopathy and proteinuria, no circulating immune complexes, and no evidence to date of sequelae of the reaction. While further investigation is ongoing, **serum-sickness-like** reactions appear to be due to hypersensitivity and more often occur during or following a second (or subsequent) course of therapy with Ceclor. Such reactions have been reported more frequently in children than in adults with an overall occurrence ranging from 1 in 200 (0.5%) in one focused trial to 2 in 8,346 (0.024%) in overall clinical trials (with an incidence in children in clinical trials of 0.055%) to 1 in 38,000 (0.003%) in spontaneous event reports. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy; occasionally these reactions have resulted in hospitalization, usually of short duration (median hospitalization = two to three days, based on postmarketing surveillance studies). In those requiring hospitalization, the symptoms have ranged from mild to severe at the time of admission with more of the severe reactions occurring in children. Antihistamines and glucocorticoids appear to enhance resolution of the signs and symptoms. No serious sequelae have been reported.
• Stevens-Johnson syndrome, toxic epidermal necrolysis, and anaphylaxis have been reported rarely. Anaphylaxis may be more common in patients with a history of penicillin allergy.
• Gastrointestinal (mostly diarrhea): 2.5%
• Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment.
• As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.
• Rarely, reversible hyperactivity, nervousness, insomnia, confusion, hypertonia, dizziness, and somnolence have been reported.
• Other: eosinophilia, 2%; genital pruritus or vaginitis, less than 1% and, rarely, thrombocytopenia and reversible interstitial nephritis.

Abnormalities in laboratory results of uncertain etiology:
• Slight elevations in hepatic enzymes.
• Transient lymphocytosis, leukopenia, and, rarely, hemolytic anemia and reversible neutropenia.
• Rare reports of increased prothrombin time with or without clinical bleeding in patients receiving Ceclor and Coumadin concomitantly.
• Abnormal urinalysis; elevations in BUN or serum creatinine.
• Positive direct Coombs' test.
• False-positive tests for urinary glucose with Benedict's or Fehling's solution and Clinitest® tablets but not with Tes-Tape® (glucose enzymatic test strip, Lilly).

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Additional information available to the profession on request from Eli Lilly and Company, Indianapolis, Indiana 46285.

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(Continued from Page 374)

February 5-9—**17th Annual Mid-Pacific Radiological Conference.** Los Angeles Radiological Society at Maui Marriott Hotel, Maui, Hawaii. Tues-Sat. 16 hrs. $395. Contact: LARS, PO Box 91215, Los Angeles 90009. (213) 827-9078.

February 6—**Intraluminal Ultrasound.** UCSD at Le Meridien Hotel, San Diego. Wed. 6 hrs. $150. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 6—**Basic Introduction to Doppler Principles.** UCSD at Le Meridien Hotel, San Diego. Wed. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 6-9—**Duplex Imaging.** UCSD at Le Meridien Hotel, San Diego. Wed-Sat. 40 hrs. $495. Contact: UCSD.

February 9-10—**Obstetric and Gynecology Sonographic Update: Focus on CNS Abnormalities.** UCSD at Le Meridien Hotel, San Diego. Sat-Sun. 10 hrs. $150. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 11-15—**Contemporary Diagnostic Imaging Featuring MRI, CT, US and Interventional Radiology.** Stanford University at Ritz-Carlton Hotel, Mauna Lani, Hawaii. Mon-Fri. 20 hrs. $515. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 1-3—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton Resort Hotel, Laguna Niguel. Fri-Sun. 18 hrs. $400. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 4-8—**Magnetic Resonance Imaging.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 27 hrs. $500. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

REHABILITATIVE/THERAPEUTIC

November 9-10—**2nd Annual Symposium-Diagnosis and Treatment of Bone and Soft Tissue Tumors: A Multidisciplinary Approach.** UCD at Hyatt Regency, Sacramento. Fri-Sat. 14 hrs. $345. Contact: UCD.

January 23-26—**6th International Symposium on Platinum and Other Metal Coordination Compounds in Cancer Chemotherapy.** UCSD at Sheraton Harbor Island East Hotel, San Diego. Wed-Sat. Contact: Cass Jones, 7916 Convoy Ct, San Diego 92111. (619) 565-9921.

February 7-9—**Biotherapy of Cancer: A Symposium for Clinicians and Nurses.** Hoag Hospital at Newport Beach Marriott. Thurs-Sat. 15 hrs. $375. Contact: Nomi Feldman, 5665 Oberlin Dr, Ste 110, San Diego 92121. (619) 453-6222.

SURGERY

October 1990-December 1990—**Temporal Bone Surgical Dissection Courses: 1990.** House Ear Institute, 5 days per month. 53 hrs. $975. Contact: Antonio de la Cruz, MD, Director of Education, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

November 12-16—**Hyperbaric Medicine.** UCI/Memorial Medical Center at Long Beach. Mon-Fri. 30 hrs. $650. Contact: Celia Loney, 2801 Atlantic Ave, PO Box 1428, Long Beach 90801. (213) 595-2000.

November 17—**C02 Surgical Laser Workshop.** Scripps Clinic and Research Foundation. Sat. 8 hrs. $600. Contact: Susan Buntjer, Box 400S, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

January 18-19-**What's New in General Surgery: 13th Annual Postgraduate Course.** UCD at Capitol Plaza Holiday Inn, Sacramento. Fri-Sat. Contact: UCD.

OF INTEREST TO ALL PHYSICIANS

October 30—**AIDS in the '90s: A Course for Primary Care Physicians.** Los Angeles Medical Association. Tues. 5.5 hrs. $75. Contact: Robert Donin, Professional Relations, (213) 483-1581, ext. 271.

November 18-21—**Putting Prevention into Practice.** SDSU at Hyatt Islandia Hotel, San Diego. Sun-Wed. 23 hrs. $140. Contact: Mickey Pagan, (619) 594-5904.

December 10-11—**Clinical Care of the AIDS Patient.** UCSF at Hyatt Regency Embarcadero, San Francisco. Mon-Tues. 13 hrs. $250. Contact: UCSF.

February 18-20—**11th Betty Ford Center Conference on Chemical Dependency.** Annenberg Center for Health Sciences. Mon-Wed. Contact: ACHSE, 39000 Bob Hope Dr, Rancho Mirage 92270. (800) 321-3690.

February 20-23—**The Practicing Physician's Approach to the Difficult Headache Patient.** Scripps Clinic and Diamond Headache Clinic at Wyndham Hotel, Palm Springs. Wed-Sat. 15 hrs. Contact: Idell Applebaum, 5252 N Western Ave, Chicago, IL 60625. (312) 878-5558.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

October 17-19—**Care of the Sick Newborn Conference.** The Children's Hospital, Denver. Wed-Fri. Contact: Conference Dept, Children's Hospital, (303) 861-6945.

October 18—**Colorado Radiological Society.** Hyatt Regency DTC, Denver. Thurs. Contact: Carol Goddard, (303) 770-6048.

October 18—**Colorado Society of Clinical Pathologists.** Denver, location to be announced. Thurs. Contact: Carol Goddard, (303) 770-6048.

October 22-26—**Rural Perinatal Traineeship (Level 1).** The Children's Hospital, Denver. Mon-Fri. Contact: Christie Sievers, (303) 861-6413.

October 27—**Rocky Mountain Hand Surgery Society.** Denver, location to be announced. Thurs. Contact: Carol Goddard, (303) 770-6048.

November 2-3—**Fort Collins Perinatal Conference.** The Children's Hospital at the Marriott Hotel, Fort Collins. Fri-Sat. Contact: Christie Sievers, (303) 861-6413.

November 9-10—**Western Slope Conference.** The Children's Hospital at the Red Lion Inn, Durango. Fri-Sat. Contact: Christie Sievers, (303) 861-6413.

November 12-16—**Rural Perinatal Traineeship (Level II).** The Children's Hospital, Denver. Mon-Fri. Contact: Christie Sievers, (303) 861-6413.

November 15—**Colorado Radiological Society.** Hyatt Regency DTC, Denver. Thurs. Contact: Carol Goddard, (303) 770-6048.

December 3-7—**Respiratory Therapy Traineeship.** The Children's Hospital, Denver. Mon-Fri. Contact: Jeff Griebel, (303) 861-6227.

January—**Perinatal Continuing Education Program.** The Children's Hospital, Denver Community Hospital-based, 40-week, self-study program for all perinatal healthcare providers. Contact: Pat Winter, (303) 861-6668.

January 17—**Colorado Radiological Society.** Hyatt Regency DTC, Denver. Thurs. Contact: Carol Goddard, (303) 770-6048.

January 26-31—**Uvetitis and Pathology.** Colorado Ophthalmological Society at Westin Hotel, Vail. Sat-Thurs. Contact: Carol Goddard, (303) 770-6048.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver, CO. (303) 270-5195.

IDAHO

February 27-March 2—**Sun Valley Program.** Pierce County Medical Society (Washington) College of Medical Education at Sun Valley. Wed-Sat. Contact: PCMS CME, 705 S 9th, No. 203, Tacoma, WA 98405. (206) 627-7137.

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Just a fraction of our time watching movies could help bring many happy endings.

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Description: Yohimbine is a 3a-15a-20B-17a-hydroxy Yohimbine-16a-carboxylic acid methyl ester. The alkaloid is found in Rubaceae and related trees. Also in Rauwolfia Serpentina (L) Benth. Yohimbine is an indolalkylamine alkaloid with chemical similarity to reserpine. It is a crystalline powder, odorless. Each compressed tablet contains (1/12 gr.) 5.4 mg of Yohimbine Hydrochloride.

Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalmic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon® is indicated as a sympathicolytic and mydriatric. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.[1,2] Also dizziness, headache, skin flushing reported when used orally.[1,3]

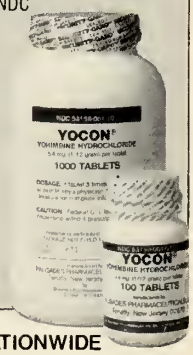
Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.[1,3,4] 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to ½ tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.[3]

How Supplied: Oral tablets of Yocon® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

Rev. 1/85



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(Continued from Page 376)

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

October 19—**The Prevention of Infectious Diseases.** Hyatt Regency Hotel, Albuquerque. Fri. Contact: Ann Winter, 601 Grand Ave, NE, Albuquerque 87102. (505) 848-8105.

October 19-20—**Cancer Update 1990.** Clarion Four Seasons Hotel, Albuquerque. Fri-Sat. Contact: UNM Office of Continuing Medical Education, PO Box 713, Albuquerque 87131. (505) 277-3942.

October 20-21—**Internal Medicine Update '90.** Inn of the Mountain Gods, Ruidoso. Contact: Deana Bernard, Providence Memorial Hospital, 2001 N Oregon St, El Paso, TX 79902. (915) 542-6284.

October 20-21—**Common Problems in Pediatric Pulmonary Disease.** Santa Fe Hilton. Sat-Sun. Contact: Joe Dean, MD, 813 N Washington, Roswell 88201. (505) 622-2606.

October 25-27—**Primary Care Update '90.** University of New Mexico Conference Center, Albuquerque. Thurs-Sat. Contact: UNM School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

October 26-28—**Review of 12 Load ECG Interpretation for the Primary Care Physician.** Presbyterian Hospital Center, Albuquerque. Contact: Anthony Sandoval, MD, New Mexico Heart Clinic, 1001 Coal, SE, Albuquerque 87106. (505) 242-2796.

October 27—**PRx: Techniques of Reducing the Frequency of Medico-Legal Lawsuits Using Paracommunication and Neurolinguistics.** Holiday Inn-Pyramid, Albuquerque. Contact: Sue Wunderland, New Mexico Physician's Mutual Liability Co, PO Box 92890, Albuquerque 87199-2890. (505) 821-9485.

November 2—**Tobacco Related Malignancies.** Los Alamos National Laboratory, Los Alamos. Fri. Contact: Peter Lindberg, MD, Los Alamos Medical Center, Los Alamos 87544. (505) 662-3524.

November 2-3—**Starting Your Practice.** La Posada Hotel, Albuquerque. Fri-Sat. Contact: S. Hill, American Medical Association, 535 North Dearborn St, Chicago, IL 60610. (312) 645-4958.

November 9-10—**The Patient, the Doctor and the Machine: A Symposium on Ethics and Technology.** Hyatt Regency, Albuquerque. Contact: Lee Stephenson, University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

October 19—**Ophthalmology Clinical Faculty Day** (Sponsor: UUMC). Fri. University of Utah, Department of Ophthalmology, Salt Lake City. Contact: (801) 581-6384.

October 19-20—**Laser Surgery—Laparoscopic Cholecystectomy** (Sponsor: UUMC). Fri-Sat. The Laser Institute, University of Utah, Salt Lake City. Contact: J. Freedman, (801) 581-7001.

October 25-26—**Laser Surgery—Gastroenterology** (Sponsor: UUMC). Thurs-Fri. The Laser Institute, University of Utah, Salt Lake City. Contact: J. Freedman, (801) 581-3293.

November 1-2—**Laser Surgery—General Surgery** (Sponsor: UUMC). Thurs-Fri. The Laser Institute, University of Utah, Salt Lake City. Contact: J. Freedman, (801) 581-3293.

November 9-11—**Laser Surgery—Laparoscopic Cholecystectomy** (Sponsor: UUMC). Fri-Sun. The Laser Institute, University of Utah, Salt Lake City. Contact: J. Freedman, (801) 581-7001.

November 16-17—**Pediatric Update** (Sponsor: UUMC). Fri-Sat. Holiday Inn, St George. Contact: (801) 581-8664.

December 7-9—**Laser Surgery—Laparoscopic Cholecystectomy** (Sponsor: UUMC). Fri-Sun. The Laser Institute, University of Utah, Salt Lake City. Contact: J. Freedman, (801) 581-7001.

January 1-6—**Arthritic Hip, Knee & Shoulder** (Sponsor: UUMC). Mon-Fri. Snowbird. Contact: (801) 581-8664.

January 15-19—**Arthroscopic Surgery 1991** (Sponsor: UUMC). Tues-Sat. Phoenix, Arizona. Contact: (801) 581-7602.

January 17-21—**Ethics and Health** (Sponsor: UUMC). Thurs-Mon. University of Utah, Olpin Union Building, Salt Lake City. Contact: (801) 581-8664.

January 25-27—**Laser Surgery—Laparoscopic Cholecystectomy** (Sponsor: UUMC). Fri-Sun. The Laser Institute, University of Utah, Salt Lake City. Contact: J. Freedman, (801) 581-7001.

February 1-3—**Pediatric Update** (Sponsor: UUMC). Fri-Sun. Jackson, Wyoming. Contact: (801) 581-7001.

February 4-8—**Surgical Pathology** (Sponsor: UUMC). Mon-Fri. Park City. Contact: K. Rassmussen, (801) 379-7178.

February 10-15—**Interventional Radiology** (Sponsor: UUMC). Sun-Fri. Park City. Contact: Judy Gallegos, (801) 581-8188.

February 10-15—**Update in Clinical Microbiology and Immunology** (Sponsor: UUMC). Sun-Fri. Park City. Contact: Midge Beckman, (801) 581-7480.

February 11-16—**Microsurgery Workshop** (Sponsor: UUMC). Mon-Sat. University Park Hotel, Salt Lake City. Contact: (801) 581-8664.

February 11-16—**Orbital & Craniofacial Surgery** (Sponsor: UUMC). Mon-Sat. Snowbird. Contact: (801) 581-8664.

February 11-17—**Family Practice Refresher Course** (Sponsor: UUMC). Mon-Sun. Salt Lake Hilton, Salt Lake City. Contact: K. Chisholm, (801) 581-7234.

February 15-19—**The 35th Anesthesiology Update** (Sponsor: UUMC). Fri-Tues. Snowbird. Contact: V. Larsen, (801) 581-6393.

February 17-20—**The 32nd Annual Ob/Gyn Update** (Sponsor: UUMC). Sun-Wed. The Yarrow, Park City. Contact: S. Martin, (801) 581-5501.

February 19-23—**Pediatric Emergency Medicine** (Sponsor: UUMC). Wed-Sun. The Marriott Hotel, Salt Lake City. Contact: (801) 588-2000.

SPONSORS OF COURSES—ABBREVIATIONS

AHA: American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.

BYUHS: Brigham Young University Health Services, McDonald Student Health Center, Brigham Young University, Provo 84602. (801) 378-2771.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 S 300 East, Salt Lake City 84101. (801) 262-3461.

DMC: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 673-9681.

HCH: Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.

(Continued on Page 380)

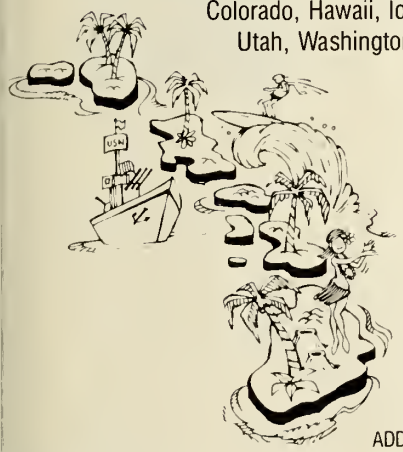
The Western Journal of Medicine

Medical Student 1991 Writing Award Competition

$1,000 CASH PRIZE!

■ Enter your original medical research or medical review article—the article must be of interest to clinicians and not previously published. The winner will receive a $1,000 cash prize and a two-year subscription to **The Western Journal of Medicine.** The winning article will be published in **WJM. Deadline to enter February 1, 1991.**

■ **WJM** is the official journal of ten western medical associations and five clinical investigation/specialty societies. This competition is only open to medical students attending school in Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington, or Wyoming.



■ **WJM** is clinically oriented, national in scope, and not confined to any single specialty. Your article must be written in **WJM** style and be of interest to our readers. If, in the judgment of the editorial board, no articles meet the standards of **WJM,** no award will be made.

ADDITIONAL RULES:

- Articles must be 3,000 to 4,000 words in length. The manuscript must be identified as submitted for consideration for this award.
- Co-authorship is permitted if all authors meet the qualifications. The $1,000 award will be divided equally among the co-authors.
- Articles must conform to **WJM's** style—our style guide, "Information for Authors," appears in the January and July issues, or you may write our editorial department for a copy of the guide.
- Articles will be judged by the editors and the editorial and advisory boards of the journal.
- The winner will be announced and the article published in **WJM.** In case of a tie, the $1,000 award will be divided equally.

DEADLINE: FEBRUARY 1, 1991.

For additional information write to:

THE WESTERN JOURNAL OF MEDICINE
Editorial Office/Award Competition
P.O. Box 7602
San Francisco, CA 94120-7602

(Continued from Page 378)

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

144: 144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave, Salt Lake City 84103. (801) 363-1221.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

SMH: St Mark's Hospital, 1200 E 3900 South, Salt Lake City 84117. (801) 268-7111.

UMA: Utah Medical Association, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUMC: University of Utah Medical Center, 50 N Medical Dr, Salt Lake City 84132. (801) 581-2258.

UVRMC: Utah Valley Regional Medical Center, 1034 N Fifth West, Provo 84604. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

VVMC: Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

October 15-16—**Laboratory Ventilation.** Portland. Mon-Tues. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

October 16-19—**Indoor Radon and Lung Cancer: Reality or Myth.** Richland. Tues-Fri. Life Sciences Center, Battelle, Pac NW Lab. (509) 376-3665.

October 18-19—**Common Office Problems.** Tacoma. Thurs-Fri. Contact: PCMS CME.

October 18-19—**Alzheimers.** Seattle. Thurs-Fri. Contact: U/W.

October 19—**24th Annual Cancer Conference: Gastrointestinal Cancer in the '90s.** Seattle. Fri. Contact: VMMC.

October 20—**Practice Update for Rural Physicians.** Seattle. Sat. Contact: VMMC.

October 24—**Sexual Dysfunction.** Seattle. Wed. Contact: Northwest Hospital, (206) 368-1622.

October 25—**Hormones of Hematopoiesis: Use of Blood Growth Factors.** Seattle. Thurs. Contact: Providence Hospital, (206) 320-2553.

November 2—**Diabetes, 1990.** Seattle. Fri. Contact: VMMC.

November 8—**Pediatrics.** Everett. Thurs. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

November 9—**Diagnosis and Treatment of Depression.** Tacoma. Fri. Contact: PCMS, (206) 627-7137.

November 9—**Medical and Surgical Update for Psychiatrists.** Seattle. Fri. Contact: VMMC.

November 9-10—**Medical Updates: Transplantation.** Seattle. Fri-Sat. Contact: U/W.

November 9-11—**Brain Injury.** Seattle. Fri-Sun. Contact: U/W.

November 10—**Regional Anesthesia Conference.** Seattle. Sat. Contact: VMMC.

November 14—**Psychiatry.** Seattle. Wed. Contact: Northwest Hospital, (206) 368-1622.

November 14-16—**Industrial Ventilation: Principles and Applications.** Seattle. Wed-Fri. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

November 15-16—**Drug Therapy.** Seattle. Thurs-Fri. Contact: U/W.

November 17—**Challenges in the Nineties: Changes in Psychiatric Care.** Seattle. Sat. Contact: Providence Hospital, (206) 320-2553.

November 29—**Hazardous Waste—Annual Refresher Course.** Seattle. Thurs. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

December 6-7—**Advanced Cardiac Life Support.** Tacoma. Thurs-Fri. Contact: PCMS CME.

December 6-7—**Surgery Update.** Seattle. Thurs-Fri. Contact: U/W.

December 7—**Practical Pediatrics.** Seattle. Fri. Contact: VMMC.

December 8—**Gastrointestinal Conference.** Seattle. Sat. Contact: Northwest Hospital, (206) 368-1622.

December 10-14—**Sampling and Evaluating Airborne Asbestos Dust.** Seattle. Mon-Fri. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

December 13-15—**6th Annual ID Conference.** Everett. Thurs-Sat. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

January 10-11—**Laboratory Safety and Health.** Seattle. Thurs-Fri. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

January 17—**Law and Medicine Symposium.** Tacoma. Thurs. Contact: PCMS CME.

January 17—**Cancer Conference.** Everett. Thurs. Contact: Pacific Northwest Medical Education Institute, (206) 258-5322.

January 19-20—**Advanced Cardiac Life Support Provider Course.** Seattle. Sat-Sun. Contact: VMMC.

January 23—**Pesticide Medicine.** Seattle. Wed. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

February 8—**Review of HIV Infections.** Tacoma. Fri. Contact: PCMS, (206) 627-7137.

February 22-23—**Arthritis Update.** Seattle. Fri-Sat. Contact: U/W.

March 1—**Recent Developments in Occupational Medicine.** Seattle. Fri. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

March 1-2—**Psychiatric and Psychological Issues in Medical Practice.** Seattle. Fri-Sat. Contact: VMMC.

March 13-15—**Spirometry Training for Worker Screening.** Seattle. Wed-Fri. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

March 14-15—**Tacoma Academy of Internal Medicine.** Tacoma. Thurs-Fri. Contact: PCMS CME.

March 15—**Inflammatory Bowel Disease.** Seattle. Fri. Contact: VMMC.

March 22-23—**Ophthalmology (WSAO)—Annual President's Meeting.** Seattle. Fri-Sat. Contact: (206) 441-9762.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

WYOMING

February 1-3—**Pediatric Update.** University of Utah School of Medicine at Jackson. Fri-Sun. Contact: UUMC, 50 N Medical Dr, Salt Lake City, UT 84132. (801) 581—2258. ◆

SPECIAL ISSUES

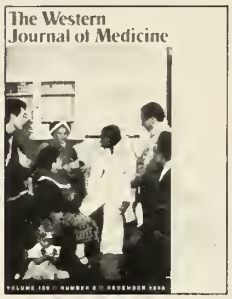
Addiction Medicine
and the Primary Care Physician

Addiction Medicine and the Primary Care Physician was conceived to be part of the initiative to expand the involvement of all specialties of medicine in the prevention and treatment of addictive disease. Topics covered include chemical dependence and the workplace, alcoholism, methadone maintenance in the treatment of opioid dependence, nicotine dependence, and treatment of cocaine dependence. David Smith MD, Special Editor, 1990.

Women and Medicine

This special issue explores both the professional side of women in medicine and the diagnosis and treatment of women patients. Topics covered include liver disease, women and AIDS, heart disease, hysterectomy, PMS, ovarian cancer, and women physicians and organized medicine. Linda Hawes Clever, MD, Special Issue Editor, 1988.

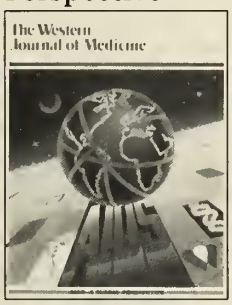
Cross-cultural Medicine



Cross-cultural medicine is devoted to the care of patients of different cultural, ethnic, or religious backgrounds. Subjects include Southeast Asian refugees in the American health care system, psychiatry and Chinese culture, health and illness in Filipino immigrants, and health care of Middle Eastern patients. M. Margaret Clark, PhD, Special Issue Editor, 1983. 2nd reprinted edition.

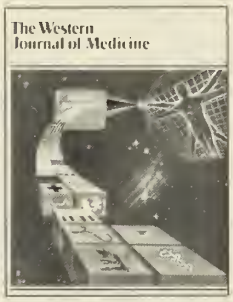
Also available:

AIDS—A Global Perspective



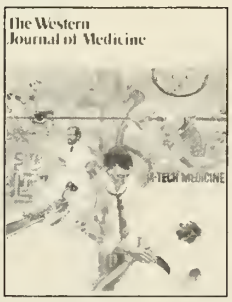
Jonathan M. Mann, MD
Special Issue Editor, 1987

Medical Informatics



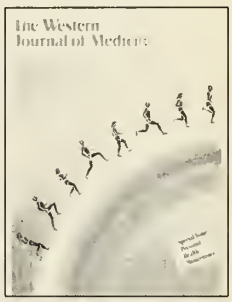
Marsden S. Blois, MD
Special Issue Editor, 1986

High-Tech Medicine



R. Paul Robertson, MD
Special Issue Editor, 1985

Personal Health Maintenance



John H. Holbrook, MD
Special Issue Editor, 1984

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Am Fam Phys 1987;36:133-140

Ceclor® Pulvules® 250 mg
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Established therapy for today's patients

For respiratory tract infections due to susceptible strains of indicated organisms

Brief Summary.
Consult the package literature for prescribing information.
Indication: Lower respiratory infections, including pneumonia, caused by *Streptococcus pneumoniae, Haemophilus influenzae,* and *Streptococcus pyogenes* (group A β-hemolytic streptococci).
Contraindication: Known allergy to cephalosporins.
Warnings: CECLOR SHOULD BE ADMINISTERED CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. PENICILLINS AND CEPHALOSPORINS SHOW PARTIAL CROSS-ALLERGENICITY. POSSIBLE REACTIONS INCLUDE ANAPHYLAXIS.

Administer cautiously to allergic patients.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics. It must be considered in differential diagnosis of antibiotic-associated diarrhea. Colon flora is altered by broad-spectrum antibiotic treatment, possibly resulting in antibiotic-associated colitis.

Precautions:
• Discontinue Ceclor in the event of allergic reactions to it.
• Prolonged use may result in overgrowth of nonsusceptible organisms.
• Positive direct Coombs' tests have been reported during treatment with cephalosporins.
• Ceclor should be administered with caution in the presence of markedly impaired renal function. Although dosage adjustments in moderate to severe renal impairment are usually not required, careful clinical observation and laboratory studies should be made.
• Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.
• Safety and effectiveness have not been determined in pregnancy, lactation, and infants less than one month old. Ceclor penetrates mother's milk. Exercise caution in prescribing for these patients.

Adverse Reactions: (percentage of patients)

Therapy-related adverse reactions are uncommon. Those reported include:
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• Rarely, reversible hyperactivity, nervousness, insomnia, confusion, hypertonia, dizziness, and somnolence have been reported.
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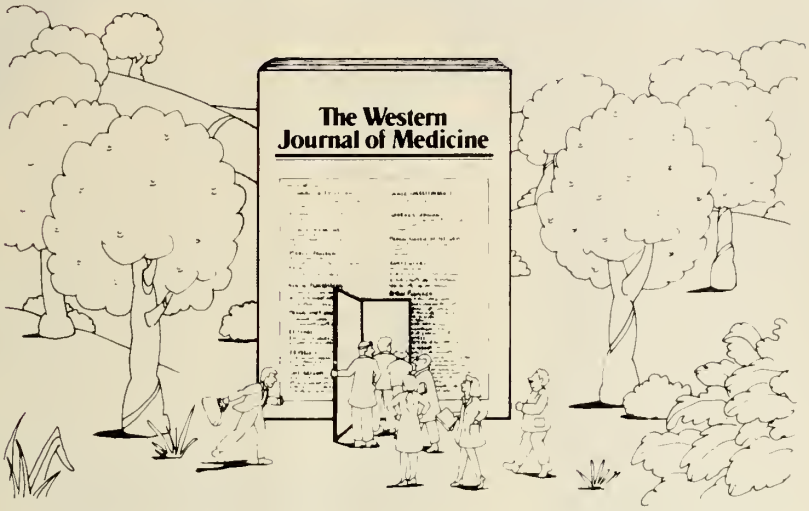

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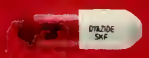

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Biomedical Science

Computed Tomography and Bronchoscopy in Chest Radiographically Occult Main-Stem Neoplasm

Diagnosis and Nd-YAG Laser Treatment in 8 Patients

ARTHUR F. GELB, MD, *Lokewood, Californio;* DENISE R. ABERLE, MD, *Los Angeles;* MARK J. SCHEIN, MD, *Lokewood, Californio;* DAVID P. NAIDICH, MD, *New York;* JOEL D. EPSTEIN, MD, *Lokewood, Californio; ond* DONALD P. TASHKIN, MD, *Los Angeles*

We studied 8 adult patients with variable symptoms of cough, dyspnea, stridor, wheezing, or hemoptysis. Fiberoptic bronchoscopy in all showed complete or nearly complete endobronchial obstruction of a main-stem bronchus by neoplasm with a mean bronchial diameter of 1.9 mm ± 1.6 mm (mean ± standard deviation). In 4 patients, a lobar bronchus was also completely obstructed. No mass was visible on chest radiographs of any patient; however, computed tomography in each showed main-stem endobronchial obstruction, lobar obstruction (4 instances in 3 patients), and in 6 patients hypoperfusion of the involved lung. Computed tomographic scan showed additional abnormalities that were unsuspected on viewing chest radiographs or at bronchoscopy, including mediastinal adenopathy in 3 patients and an extraluminal tumor component in 4. After therapy with Nd-YAG laser, main-stem airway diameter increased to a mean of 9.6 mm ± 1.0 mm ($P<.05$) and pulmonary functions improved. Results suggest the complementary role of computed tomography and fiberoptic bronchoscopy in the detection and laser-treatment planning of chest radiographically occult severe neoplastic obstruction of the main-stem bronchus.

(Gelb AF, Aberle DR, Schein MJ, Naidich DP, Epstein JD, Tashkin DP: Computed tomography and bronchoscopy in chest radiographically occult main-stem neoplasm—Diagnosis and Nd-YAG laser treatment in 8 patients. West J Med 1990 Oct; 153:385-389)

Several studies have addressed the use of computed tomography (CT) as a noninvasive diagnostic technique for evaluating normal[1-3] and abnormal airways.[4-9] It is important to define the role of computed tomography in detecting and characterizing obstructing lesions of the central airways that may be amenable to laser resection. Previous studies have compared CT with bronchoscopy in patients having abnormal chest radiographs and suspected lung cancer. In our study we compared CT with fiberoptic bronchoscopy in eight patients with nondiagnostic chest radiographs in whom extensive unilateral main-stem bronchial obstruction was documented bronchoscopically. Clinical and physiologic improvement occurred after Nd-YAG [neodymium-yttrium-argon-garnet] laser treatment of the obstruction in all eight patients. Results show that despite a normal chest radiograph, CT can detect significant central airway abnormality. In addition, CT may define mediastinal involvement, additional sites of obstruction, or an extraluminal tumor component that is unsuspected from bronchoscopy results. Computed tomography and fiberoptic bronchoscopy provide complementary information in evaluating main-stem neoplastic endobronchial obstruction.

Patients and Methods

We reviewed the clinical, radiographic, and bronchoscopic findings of eight adult patients with main-stem bronchial neoplasm and a normal chest radiograph. All eight were clinically symptomatic with variable and intermittent cough, dyspnea, stridor, wheezing, or hemoptysis. Five patients (1 through 5, Table 1) are included from a previous study[10] of the physiologic characteristics of main-stem bronchial obstruction. In all patients, chest radiographs, CT scans, pulmonary function tests, fiberoptic bronchoscopy, and Nd-YAG laser therapy were carried out.

The chest radiographs and CT scans were interpreted independently by three radiologists who had no other clinical knowledge of these patients. Chest radiographic examinations consisted of posteroanterior and lateral projections using a high-kilovoltage technique. Chest CT scans were done on various clinical scanners and consisted of contiguous 8- to 10-mm-thick sections at suspended maximal inspiration. Intravenous contrast material was infused in six patients, with the bolus technique used in four. Because Naidich and co-workers have shown that CT cannot distinguish among mucosal, submucosal, and peribronchial lesions,[5] we defined bronchial obstruction as predominantly intraluminal or extraluminal, according to the descriptions of Zwirewich and associates.[9] Bronchial obstruction was defined as predominantly intraluminal if the CT scan showed an endobronchial mass surrounded by air and causing little or no deformity, encasement, or thickening of the bronchial wall. Conversely, the obstruction was considered predominantly extraluminal if there was either a mass surrounding the bronchus at the level of obstruction associated with an irregular contour and thickening of the bronchial wall or encasement of the bronchus with tumor.[9] The presence of a mass adherent to an occluded bronchus did not preclude a predominantly intraluminal obstruction if the obstructing mass met our criteria for intraluminal disease and did not distort or narrow the bronchus by compression.[9]

Bronchial obstructions were also classified according to

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their appearance on fiberoptic bronchoscopy. Bronchial occlusion was classified as intraluminal if there was narrowing or obstruction of the bronchus by an exophytic lesion. Alternatively, airway narrowing or obstruction without an intraluminal exophytic mass was classified as extraluminal and included submucosal and extrinsic lesions. In addition, the airway diameter at the point of occlusion was visually estimated at the time of bronchoscopy by comparison with the reference diameter of the fiberoptic or rigid bronchoscope. Follow-up bronchoscopic evaluation was done in all patients within three weeks of Nd-YAG laser therapy.

Spirometry including maximum expiratory and inspiratory flow-volume loops[10] was done in each patient before and at least three weeks after laser therapy using a 13.5-liter water-sealed spirometer with potentiometer (Warren E. Collins, Braintree, Mass). The results were compared with previously published standards.[11] Before laser treatment, detailed informed consent was obtained from each patient in accordance with the guidelines of the US Food and Drug Administration, California Patients' Bill of Rights, and local hospital institutional review committees. Surgical resection, chemotherapy, and external-beam radiotherapy were rejected in favor of laser treatment if patients had severe symptoms from localized airflow obstruction requiring immediate palliative relief, notably abnormal lung function, histologic findings indicating that the neoplasm was unlikely to respond to chemotherapy or radiotherapy, mediastinal or distant metastases, or a poor state of health.

Results

Chest radiographs were interpreted as normal in seven of the eight patients. In one, focal hyperlucency was suggested in the left lower lobe (Figure 1). None of the patients had a history of obstructive lung disease. Computed tomographic scans in each patient showed predominantly intraluminal obstruction of a main-stem bronchus, although in four an extraluminal component was also seen (Table 1). In three patients (four occurrences), obstruction of a lobar bronchus was seen distal to the occluded main-stem bronchus. In addition, hypoperfusion of the involved lung, appearing as decreased attenuation and a reduction in the number and caliber of vascular structures, was observed in six of eight patients on CT (Figure 2); in only one patient was hyperlucency also visible on chest radiographs. In three, CT showed unsuspected mediastinal lymphadenopathy.

Bronchoscopic assessment in all eight patients was concordant with CT observations of intraluminal tumor occluding a main-stem bronchus; however, in none of the four patients in whom CT scans showed extraluminal tumor was the latter observed at endoscopy. After laser therapy and recannulation of the obstructed main-stem bronchus, occlusions of lobar bronchi distal to the main-stem occlusion were seen four times in three patients, but in no case was laser therapy attempted at the lobar level.

TABLE 1.—*Comparison Between Fiberoptic Bronchoscopy (FOB) and Computed Tomography (CT) in Patients With Bronchial Obstruction and Normal Chest Radiographs*

		Diameter, mm		Method and Location of Lesion	
Patient	Site	Before Laser Therapy	After Laser Therapy	FOB	CT
1	LMS	0	10	I	I
2	RMS	1	9	I	I,E
	RUL	0	Not done	I,E	I,E
3	RMS	1	9	I	I
4	RMS	1	10	I	I,E
	RUL	1	Not done	I,E	I,E
5	LMS	4	11	I	I,E
6	LMS	4	8	I	I
	RML	0	Not done	E	E
	RLL	0	Not done	E	E
7	LMS	2	10	I	I
8	RMS	1	9	I	I,E

E = extraluminal, I = intraluminal, LMS = left main-stem bronchus, RLL = right lower lobe bronchus, RML = right middle lobe bronchus, RMS = right main-stem bronchus, RUL = right upper lobe bronchus

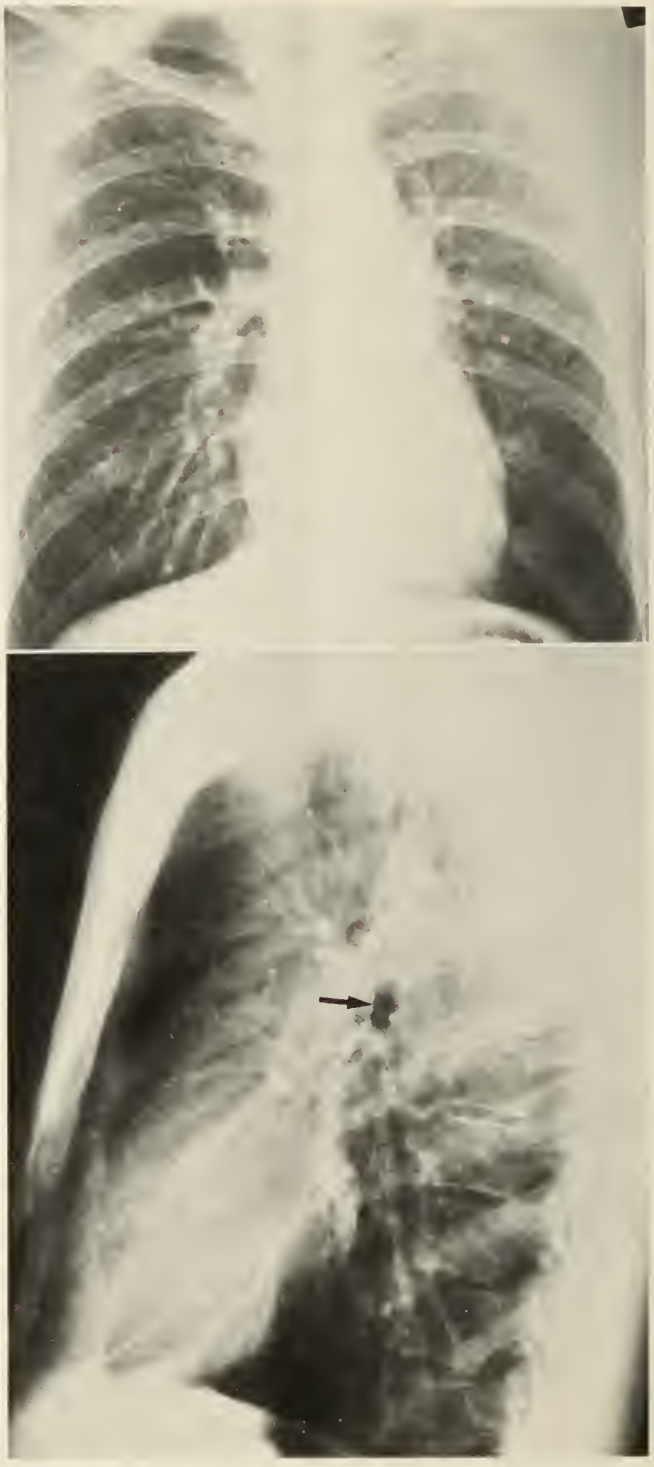

Figure 1.—On posteroanterior **(top)** and lateral **(bottom)** chest radiographs of patient 1, no mass is visible, although focal hyperlucency is suggested in the left lower lobe. The left main stem-left upper lobe bronchus is patent **(arrow)**.

All patients underwent Nd-YAG laser treatment of the occluded main-stem bronchus. The presence of a concomitant extraluminal tumor in four patients did not prevent short-term success from the Nd-YAG laser therapy. By direct bronchoscopic estimates, the mean main-stem bronchial diameter was 1.9 mm ± 1.6 mm (± 1 standard deviation) before laser therapy; after laser therapy the mean diameter increased to 9.6 mm ± 1.0 mm ($P<.05$). In addition, as previously reported,[10] physiologic improvement was documented in each case. After laser therapy, the forced vital capacity increased from 52% ± 18% of predicted to 88% ± 15.7% of predicted ($P<.05$), and the forced expiratory volume in one second increased from 49% ± 12% of predicted to 80% ± 15% of predicted ($P<.05$). Moreover, after relief of the main-stem obstruction, the descending limb of the maximum expiratory flow-volume curve shifted in almost parallel fashion to the right of the pretreatment curve in two patients (Figure 3). All eight reported symptomatic improvement after laser treatment.

Discussion

Our study of eight adult patients shows that CT and fiberoptic bronchoscopy are complementary in detecting severe unilateral main-stem bronchial obstruction in patients with normal chest radiographs. The diagnosis of significant central airway obstruction is often obscure from a clinical, physiologic , and imaging standpoint. Despite substantial obstruction at the level of the trachea[12,13] or main-stem bronchus,[10] symptoms may be variable and intermittent and may include cough, dyspnea, stridor, wheezing, or hemoptysis. These symptoms are relatively nonspecific or may occur in the setting of diffuse obstructive lung disease and as such are often overlooked.

The frequency of chest radiographically occult endobronchial malignancy in the presence of hemoptysis has been variably reported at 4%,[14] 10%,[15] and 33%,[16] depending on the characteristics of the cohort examined. The eight patients with normal chest radiographs herein reported represent 7.4% of all patients referred for laser treatment of unilateral main-stem bronchial obstruction, the others all having had abnormal chest radiographs. Risk factors suggesting bronchogenic carcinomas as the cause of hemoptysis in patients with a normal chest radiograph include an age of 40 years or more, significant smoking history, and hemoptysis for longer than a week.[14] Fiberoptic bronchoscopy is considered to be indicated in the evaluation of such persons,[14-16] but this recommendation is not universally accepted.[17] By comparison, the Early Lung Cancer Cooperative Study reported a 0.2% prevalence of chest radiographically occult endobronchial malignancy using screening sputum cytologic findings in asymptomatic high-risk patients.[18]

Computed tomography has been advocated as a noninvasive technique for evaluating the airways. The role of CT in the clinical management of airway disease has been addressed in various studies by comparison with chest radiography and fiberoptic bronchoscopy. In a retrospective study of 50 patients with radiographic segmental or lobar atelectasis, Woodring compared findings on CT with those of chest radiography, using as the standard of reference all clinical data including findings at bronchoscopy, thoracotomy, or follow-up clinical evaluation.[4] Computed tomography correctly identified all 27 obstructing neoplasms based on the observations of center hilar mass or focal bronchial abnormality. Computed tomography had 100% sensitivity and 87% specificity. Of significance, in 15 patients (30%), the diagnosis was not apparent from the clinical, historical, or chest radiographic information. In these patients, CT diagnosed all of three missed carcinomas and successfully excluded neoplasm in 10 of the other 12 patients, giving a correct diagnosis in 87% of cases in which the cause of atelectasis had been unknown.

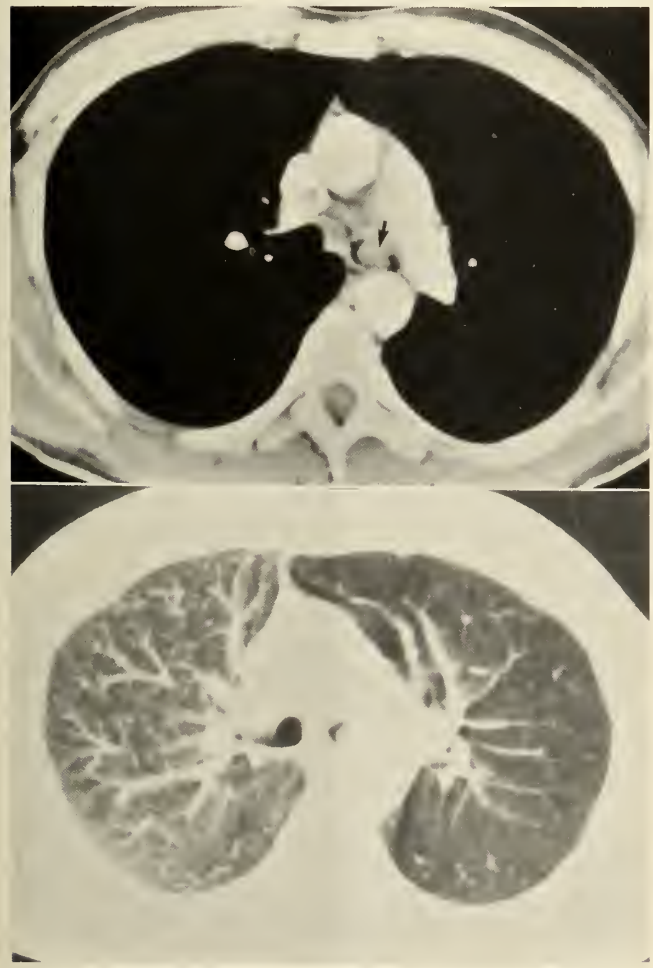

Figure 2.—On intravenous contrast-enhanced computed tomographic scans, shown at both soft tissue **(top)** and lung **(bottom)** windows, there is an endobronchial mass protruding from the anterior wall of the left main-stem bronchus causing near-complete obstruction of the airway **(arrow)**. There is no significant extraluminal tumor component. The lung window shows dramatic hypoperfusion of the left lung with relative hyperlucency and a decrease in the number and caliber of intrapulmonary blood vessels.

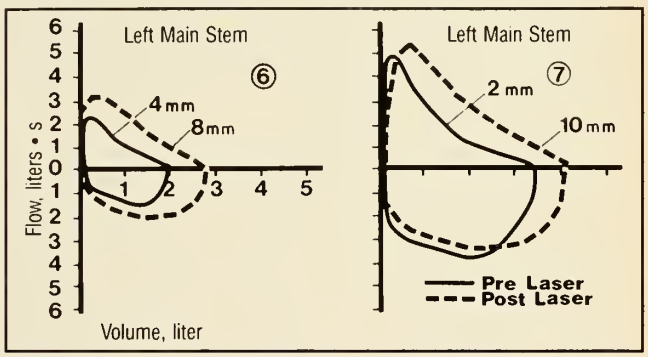

Figure 3.—Maximum inspiratory and expiratory flow-volume loops of patients 6 and 7 show substantial improvement in forced vital capacity and flow rates following laser therapy. Note the nearly parallel shift of the descending limb of the expiratory flow-volume loop to the right after laser therapy. Before laser therapy, there is mild slowing of expiratory flow at lower lung volumes (patient 7) and a reduced forced vital capacity. The total lung capacity was normal and essentially unchanged before and after laser therapy.

In a retrospective study of 64 patients with abnormal chest radiographs and focal airway abnormalities, Naidich and colleagues found good correlation between CT and fiberoptic bronchoscopy in the detection of disease in 59 patients (92% of cases).[5] The CT technique included thin sections (1- to 5-mm thick) through suspicious-looking bronchi and bolus injections of intravenous contrast as indicated to clarify hilar vascular anatomy. In no patient was a diagnosis of a malignant lesion missed by CT. Nevertheless, it failed to detect three cases of malignant submucosal extension of tumor involving the left main-stem bronchus. Conversely, five lesions detected on CT were not identified at bronchoscopy; in each case, the findings were distal to abnormal airways in patients subsequently proved to have carcinoma. Based on a predefined radiographic classification, CT was inaccurate in distinguishing focal endobronchial, submucosal, or extraluminal airway lesions. Only irregular bronchial narrowing or a discrete intraluminal filling defect proved specific for endobronchial disease. Naidich and co-workers concluded that despite the inaccuracy in predicting specific bronchoscopic findings, CT evaluation was complementary to fiberoptic bronchoscopy both in detecting lesions and delineating the extent of extraluminal airway disease. This information has obvious importance when transbronchial needle-aspiration biopsy or laser therapy is contemplated.

Webb and associates also noted a close correlation between bronchial abnormalities as identified by CT and fiberoptic bronchoscopy in a study of 30 patients with abnormal chest radiographs and carcinoma.[6] Colice and colleagues concluded, however, that CT (and chest radiographs) could not accurately identify endobronchial abnormalities in patients with known or suspected lung cancer.[7] Unfortunately, no attempt was made in the last study to use thin sections to assess airway disease, nor was the usefulness of intravenous contrast material evaluated.

In patients for whom laser therapy is contemplated, the applications of CT for the pretreatment assessment of the lesion and its relationship to adjacent structures and for predicting outcome relative to bronchoscopy have been described.[8,9] Pearlberg and associates concluded that CT was useful for delineating vascular structures adjacent to the planned area of photoresection for malignant lesions, but that for benign stenoses CT provided no more information than conventional radiography that was not available to an endoscopist by direct inspection.[8] In our study, topographic relationships between tumor and vessels as delineated on CT were important in planning laser therapy. In general, tumors proximate to or invading a major vessel may predispose to bleeding, but by directing the laser along the axial length of the bronchus, complications of bleeding, perforation, or both may be minimized.

Zwirewich and co-workers compared CT with bronchoscopy in 20 patients with complete bronchial obstruction in the evaluation of the extent of disease and in the prediction of laser therapy outcome.[9] The chest radiographs in these patients were all abnormal. Bronchial obstruction shown by both CT and bronchoscopy was visually categorized as predominantly intraluminal or extraluminal, and a positive response was defined as 50% or greater relief of obstruction on follow-up bronchoscopy. Nine patients had predominantly intraluminal obstruction as seen by both methods; of these, eight had a positive response to laser therapy. Conversely, in ten patients with predominantly extraluminal neoplasm as shown on CT, bronchoscopy incorrectly suggested intraluminal tumor in five. Of these ten, only two had a positive response to laser photoresection. The difference in response between the two groups as categorized by CT was significant ($P<.01$). The authors concluded that CT is superior to bronchoscopy in evaluating the extent of extraluminal compression by tumor and that the presence of predominantly extraluminal tumor on CT correlates with a poor response to laser therapy.

The characteristics of our patients differ from those of previous studies in that all of the chest radiographs were initially interpreted as normal. Computed tomography was done as an initial means of determining the site(s) of obstruction and the relative intraluminal and extraluminal tumor components, thereby serving as a guide to laser resection.[8,9] In four instances, CT showed additional sites of lobar obstruction distal to proximal main-stem lesions. On CT and bronchoscopy, all main-stem bronchial lesions had a predominantly intraluminal component, although in four patients CT showed unsuspected extraluminal disease. Laser therapy resulted in morphologic and physiologic improvement and lessening of symptoms in all patients. Laser therapy may have been successful because there was an identifiable intraluminal component in all. As suggested by Pearlberg and associates, CT provided a cross-sectional map of the relationship of vascular structures to mass, which directly affected the bronchoscopist's approach to laser therapy.[8]

In six patients, obvious hyperlucency and a decrease in vessel caliber were seen in the lung distal to bronchial obstruction on CT. Because of greater contrast resolution, these observations were much more readily apparent on CT than on chest radiographs. When there is a central obstructing bronchial lesion, hyperlucency results from reflex vasoconstriction and reduced perfusion to poorly ventilated, hypoxic bronchopulmonary segments. Air trapping and focal hyperinflation may occur, but they are visible only on expiratory studies and do not contribute to the hyperlucency seen on images obtained at maximal inspiration.[19]

Pulmonary function studies, including maximum expiratory and inspiratory flow-volume curves, may be nondiagnostic in patients with central airway obstruction in that they fail to show characteristic flow-limiting plateaus. This is particularly the case in patients with underlying chronic obstructive lung disease in whom the physiologic manifestations of diffuse intrathoracic airflow obstruction may mask airflow limitation resulting from central airway obstruction.[10,12,13]

After successful laser therapy for unilateral main-stem bronchial obstruction, we noted improvement in the forced vital capacity without a change in the initially normal or nearly normal total lung capacity, along with a parallel shift of the descending slope of the maximum expiratory flow-volume curve (Figure 3). These observations suggest that main-stem bronchial obstruction causes reversible parallel loss of functioning lung units. If the lung function from the uninvolved lung is normal, the resultant descending slope of the maximum expiratory flow-volume curve will be linear and normal (patient 6, Figure 3). Alternatively, if lung function from the uninvolved lung is abnormal, or if the involved unilateral obstruction is partial, the descending slope will be alinear; the slower emptying unit would result in lower flow rates, especially at lower lung volumes. We suspect that the latter phenomenon occurred in patient 7 (Figure 3). A more detailed physiologic explanation of unilateral main-stem bronchial obstruction has recently been proposed.[10]

In 1989 Chetty and colleagues reported improved aeration in only 21% of patients after radiation therapy for

atelectasis due to malignant bronchial obstruction.[20] By comparison, the improvement seen in our study reflects a favorable role of laser therapy in bronchial obstruction in the absence of atelectasis.

In summary, our study suggests that chest CT and fiberoptic bronchoscopy have complementary roles in the diagnosis and treatment planning of chest radiographically occult main-stem bronchial obstruction. It is evident that significant central airway obstruction and resulting distal hypoperfusion can be identified on CT when radiographic films show no abnormalities. These observations take on added importance because symptoms and pulmonary function tests may also be nondiagnostic.

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Articles

Botulism Among Alaska Natives
The Role of Changing Food Preparation and Consumption Practices

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Alaska Natives have one of the highest rates of food-borne botulism worldwide. All outbreaks have been associated with the consumption of native foods, but in recent years outbreaks have occurred in previously unaffected areas and have involved new food items. Five botulism outbreaks occurred between 1975 and 1985 in an area of southwestern Alaska without previous confirmed outbreaks and among one ethnic group, the Yupik Eskimo. Of the 5 outbreaks, 3 were associated with fermented beaver tail, a nontraditional native food recently introduced into the region. Preparation techniques vary widely within villages and among ethnic groups. Traditional fermentation techniques have changed over the past 50 years; current preparation methods used by some families and ethnic groups may be more favorable for *Clostridium botulinum* growth. Prevention efforts should be targeted at high-risk subgroups of Alaska Natives who appear to have modified traditional practices and increased their risk of food-borne botulism.

(Shaffer N, Wainwright RB, Middaugh JP, et al: Botulism among Alaska Natives—The role of changing food preparation and consumption practices. West J Med 1990 Oct; 153:390-393)

Alaska Native Americans have one of the highest rates of food-borne botulism in the world. Despite the expectation that outbreaks would decrease with increasing westernization and education campaigns,[1] the annual number of outbreaks has remained relatively constant since the 1970s,[2] and recent outbreaks in Alaska have occurred in previously unaffected regions.

The epidemiology of Alaska Native botulism is complex, with seasonal, demographic, and food-vehicle differences in the pattern of outbreaks.[2] Outbreaks associated with fermented fish heads ("stinkheads") and fish eggs ("stink eggs") occur in the summer, while outbreaks associated with fermented whale ("muktuk"), fermented beaver tail ("stinky tail"), and fermented seal flipper occur throughout the year. Most outbreaks have occurred among Eskimos in western Alaska and among Native Americans in the southeast.[2,3] The extent to which variations in fermented food preparation and consumption practices might account for some of these differences has not been described.

The first confirmed botulism outbreak in the Bristol Bay area of southwestern Alaska occurred in 1975. News of this event spread widely throughout Bristol Bay. Because of concern that the use of plastic containers might favor *Clostridium botulinum* growth, an education campaign was conducted warning of the dangers of using plastic bags to prepare or store fermented foods.[1] After several years without additional outbreaks, four outbreaks occurred in Bristol Bay in 1984 and 1985. Because botulism appeared to be a relatively new phenomenon in this area, we investigated these outbreaks to learn more about the risk factors related to food preparation and consumption practices.

Background

Bristol Bay (104,700 km^2 [40,425 sq mi]) has a native population of 4,137 (1985 census) Yupik Eskimos, Aleuts, and Athabascan Indians living in villages of 30 to 500 persons (Figure 1). Dillingham, the largest town in the region, has a year-round mixed Alaska Native and white population of 1,500, which increases to 10,000 during the salmon fishing season of June through August.

With the introduction of western conveniences and consumer goods, Alaska Native life-styles have changed dramatically over the past 25 years. The patterns of village life, however, are still largely determined by the seasonal activities of hunting, fishing, and gathering. In summer, most villagers move to temporary fishing camps, where the year's catch is preserved for storage by drying, salting, or freezing. During this time, salmon fish heads and other native foods are traditionally fermented and consumed.

Methods

Surveillance data from the Arctic Investigations Laboratory, Centers for Disease Control, and Alaska Division of Public Health were reviewed. A confirmed outbreak of botulism was defined as a suggestive illness in one or more persons with a common food ingestion and either botulism toxin recovered from serum or food, or *C botulinum* identified in a suspected patient's stool specimen.[2]

In 1987 we reviewed the original Bristol Bay outbreak investigation reports and interviewed implicated food preparers about their methods of preparation. Standardized questionnaires were administered to community health aides from 20 of the 29 villages in the region, to Alaska Native high school students from four Eskimo villages, and to a sample of food preparers not associated with outbreaks from three affected and three unaffected villages. Questions were asked about the type of fermented foods eaten, the methods of preparation, and changes in practices over time. In addition, open-ended interviews were conducted with elderly Alaska Natives. The χ^2 and Fisher's exact tests were used to compare survey responses. Differences between groups were considered significant at $P \leq .05$ (two-tailed).

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TABLE 1.—*Suspected and Confirmed Botulism Outbreaks in Bristol Bay, Alaska, 1947-1986*

Date	Village	Ethnic Group	Cases, No.	Sex Female, No.	Deaths, No.	Vehicle	Container	Toxin Type
2/73*....	Clark's Point	Yupik	3	3	0	Beaver tail	Plastic	..
3/75†....	New Stuyahok	Yupik	3	3	2	Beaver tail	Plastic	A
3/84.....	Goodnews Bay	Yupik	1	1	0	Beaver tail	Wood	B
8/84.....	Manokotak	Yupik	1	1	0	Seal flipper	Wood	E
7/85.....	Ekuk	Yupik	8	8	0	Fish heads	Wood	E
7/85.....	Dillingham	Yupik	7	4	0	Beaver tail	Wood	B

*Unconfirmed outbreak
†First confirmed outbreak in Alaska associated with fermented beaver tails.

Results

Descriptive Epidemiology

Between 1947 and 1972, there were 21 confirmed or suspected Alaska Native botulism outbreaks, a mean of 0.8 outbreaks per year. Most (90%) occurred on the west and southeast coasts. During 1973 to 1986, with active surveillance, 38 confirmed outbreaks were detected (Figure 2), a mean of 2.7 outbreaks per year. While type E botulism is most common, since 1973 types A and B have accounted for 12 (32%) of 38 outbreaks (Figure 2).

Of 38 confirmed outbreaks in Alaska since 1973, 5 (13%) occurred in the Bristol Bay region. In addition to these five confirmed outbreaks, there was one unconfirmed outbreak in Bristol Bay (Table 1). These outbreaks occurred in 6 (33%) of 18 Yupik villages; no outbreaks were reported in the 11 Aleut and Athabascan villages (Figure 1). The confirmed Bristol Bay outbreaks involved 20 cases (range, 1 to 8 per outbreak), 17 (85%) in women. All cases occurred in adults 24 to 69 years of age (median 41.5 years). Two deaths occurred during the 1975 outbreak (case-fatality ratio 10%). The average annual incidence of confirmed botulism cases among Alaska Natives in Bristol Bay during 1973 to 1986 was 3.7 per 10,000 compared with 2.9 per 10,000 statewide.

Three of the five confirmed outbreaks and one unconfirmed outbreak in Bristol Bay were due to fermented beaver tail. No other outbreaks in Alaska were associated with beaver tail. Three of the four beaver tail outbreaks occurred in the early spring, during beaver trapping season.

The Bristol Bay Area Outbreaks

New Stuyahok. In March 1975, signs of acute botulism poisoning developed in three women, ages 42 to 57 years, after they ate fermented beaver tail. Two of the women died of respiratory failure within 24 hours after the symptoms began. The 53-year-old female preparer had wrapped fresh beaver tails in a plastic bag and placed them near a warm stove for more than two weeks.

Goodnews Bay. In March 1984, type B botulism developed in a 30-year-old woman after she ate fermented beaver tail prepared by a 50-year-old woman. Fresh beaver tails were packed in moss and grass in a wooden barrel and set outside for two weeks where it was "warm enough so it wouldn't freeze."

Manokotak. In August 1984, type E botulism developed in a 35-year-old woman after she ate an uncooked, fermented seal flipper. Two seal flippers had been placed in a wooden bucket, covered with moss, and allowed to ferment in the shed house for "about five days in a warm place."

Ekuk. In July 1985, a type E botulism outbreak followed a July 4th feast of fermented salmon fish heads. There were eight confirmed cases, all in women ranging in age from 24 to 69 years. At the time, most of the men in the village were away fishing. The 41-year-old food preparer had been taught to ferment foods by her mother, but had not prepared such foods in many years. As was customary in her family, she placed more than 50 king salmon and red salmon fish heads in a wooden barrel, added fish entrails, and covered the top with a canvas cloth. Instead of placing the

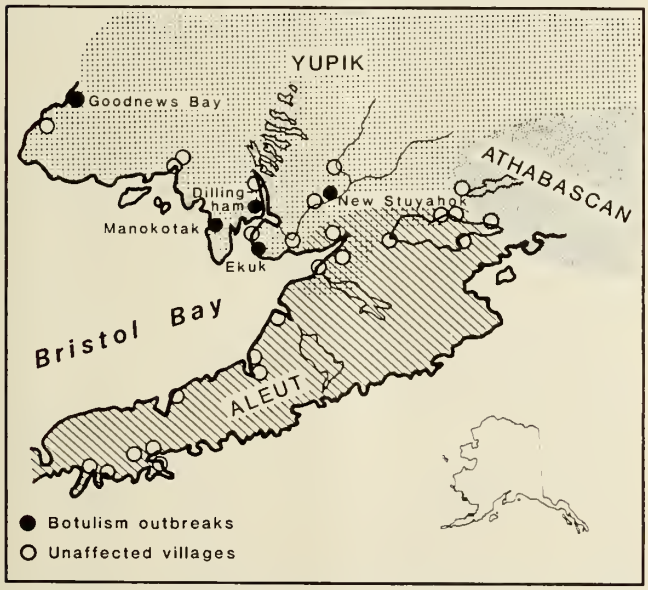

Figure 1.—The map shows the Bristol Bay area of southwestern Alaska, with distribution of ethnic groups and locations of confirmed botulism outbreaks.

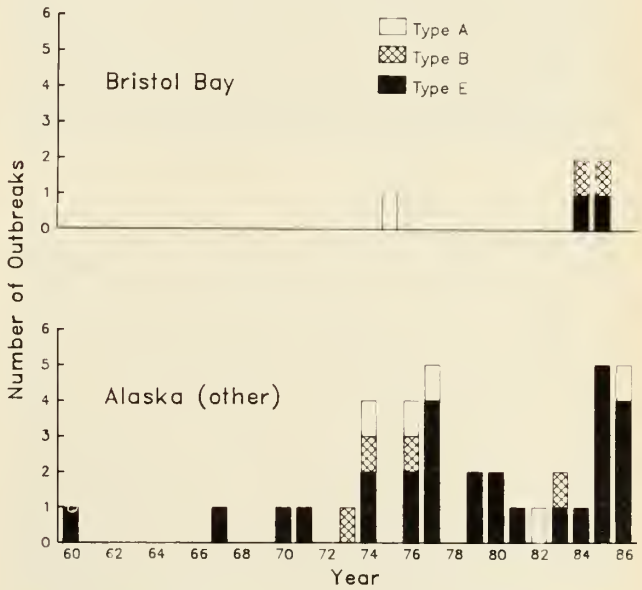

Figure 2.—The graph indicates toxin-confirmed botulism outbreaks in Alaska, by type, 1960-1986 (active surveillance was begun in 1973).

barrel in a pit in the ground for a week as was usually done by her family, she set the barrel out in the open above ground for more than two weeks. In retrospect, she expressed concern that the sun-exposed barrel may have gotten too hot. She recalled having been warned as a child that the sun's rays had a "death meaning" and that fermented foods needed to be kept away from the "killing rays of the sun."

Dillingham. In July 1985, a 59-year-old Eskimo woman prepared fermented beaver tails from frozen tails gathered several months before. The tails were placed in a wooden barrel, covered with moss and water, and set in the drying shed "for about two weeks." At least 15 people ate slices of the beaver tail; symptoms of botulism developed in 7, and 3 had type B toxin detected in their serum. The preparer said she had made beaver tails once or twice a year for 10 years, usually with fresh tails collected during the spring beaver run. She learned to ferment beaver tail from neighbors because her mother and grandmother did not prepare this food.

Surveys of Food Handling Practices

The results of the village health aide survey show that fermented food preparation practices in Bristol Bay vary by village and are most widespread among the Yupik ethnic group (Table 2). Although fermented fish heads are prepared by at least one family in all Yupik villages and most non-Yupik villages, fermented beaver tails were prepared in eight (67%) Yupik villages but in none of the non-Yupik villages ($P<.01$). Currently, most adults were said to eat fermented food in six (50%) Yupik villages but in none of the non-Yupik villages ($P=.04$). Fifteen years ago a majority of families in all Yupik villages and in only half of non-Yupik villages prepared their own fermented foods ($P=.01$).

A survey of 45 Alaska Native high school students from four Yupik villages also showed that the consumption of fermented food was common in that group and varied by family and age. More than half (51%) of families were reported to regularly prepare fermented foods; 71% of parents and 80% of grandparents regularly ate fermented foods, in contrast with 15% of students.

A survey of 24 Yupik food preparers from six villages revealed notable individual differences in preparation practices (Table 3). All prepared fermented fish heads, but only 10 (42%) had prepared beaver tails. Ten prepared fermented foods no more than once a year, 13 prepared them two to five times a year, and 1 prepared them more than five times a year (not shown).

Ethnographic Observations

Local fermentation methods appear to have changed within the living memory of elderly Yupik. Interviews with 12 elderly Yupik indicated that fish heads were traditionally fermented in clay pits dug in the ground; families used the same pit each year. About 50 years ago, large wooden barrels became available and were filled with fish heads and placed into the pits. Recently, many families stopped using these pits and, instead, set the barrels out above ground, usually in the shade. Some preparers now use plastic bags or buckets, and some set these indoors to speed fermentation.

Fermented food practices are distinctly different among the other ethnic groups in Bristol Bay. The Athabascans ferment fish by floating a string of fish heads in the river for one to two weeks. Among the Aleuts, fermented foods were more common a generation ago but even then were not prepared by all families. Today the few families preparing fermented foods customarily place a wooden barrel filled with fish heads into a pit in the ground in September, at the end of the fishing season; an Aleut reported that they believe that it is too hot in July to make fermented foods.

While Eskimos have long eaten boiled beaver tail stew, fermented beaver tail appears to be a local innovation introduced into several Yupik villages in Bristol Bay in the 1960s. One elderly Eskimo claimed that he had "invented" fermented beaver tail 20 years ago after finding a beaver carcass that had fermented naturally during the spring thaw. Unlike fermented fish heads, fermented beaver tail is not prepared or eaten by the Athabascans or Aleuts, and no traditional method for its preparation could be documented.

Discussion

Fermented foods have caused botulism in several cultures in the circumpolar regions.[4-8] In Alaska, while all botulism outbreaks have been associated with fermented or traditional foods consumed by Alaska Natives, recent out-

TABLE 2.—*Results of a Village Health Aid Survey: Reported Fermented Food Practices in 20 Bristol Bay Villages**

Characteristic	Yupik Villages (N = 12) No. (%)	Other Villages† (N = 8) No. (%)	P Value‡
Type of fermented food prepared (by at least one family in village)			
Fish heads	12 (100)	6 (75)	NS
Fish eggs	3 (25)	1 (13)	NS
Beaver tail	8 (67)	0 (0)	<.01
Whale flipper	1 (8)	0 (0)	NS
Seal flipper	3 (25)	0 (0)	NS
Most families in village now prepare fermented foods	4 (33)	0 (0)	NS
Most families in village prepared fermented foods 15 yrs ago	12 (100)	4 (50)	.01
Most adults in village eat fermented foods	6 (50)	0 (0)	.04
At least 25% of children in village eat fermented foods	4 (33)	0 (0)	NS
Most children speak English with parents	6 (50)	8 (100)	.04

*Survey asked what percent of families in village followed a given practice.
†5 Aleut and 3 Athabascan villages.
‡2-Tailed Fisher's exact test (NS = not significant).

TABLE 3.—*Fermented Food Preparation Methods: Survey of 24 Food Preparers in 6 Yupik Eskimo Villages*

Customary Technique	Fish Heads (N = 24) No. (%)	Beaver Tail (N = 10) No. (%)
Fermentation Chamber		
Hole in ground	3 (13)	0
Wooden barrel in ground	9 (38)	0
Wooden barrel above ground	10 (42)	5 (50)
Plastic bucket above ground	2 (8)	5 (50)
Items Added		
Salt	5 (21)	3 (30)
Fish guts	7 (29)	0
Covered with moss	5 (21)	9 (90)
Duration of Fermentation, wk		
<1	7 (29)	2 (20)
1-2	15 (63)	6 (60)
>2	2 (8)	2 (20)

breaks have occurred in new areas and have been caused by new food vehicles, suggesting that local modifications in the handling of these foods may determine the risk of botulism. In Bristol Bay, we found that fermentation practices vary among ethnic groups and among families in the same village and that traditional fermentation techniques have been modified. Among the Yupik, who experienced all of the local botulism outbreaks, containers set above ground have replaced the traditional covered pit in the ground; time and temperature vary widely. In contrast, the few Aleuts who prepare fermented foods follow traditional techniques that promote slow, low-temperature fermentation, and the Athabascans practice an entirely different method, which also keeps fermentation temperatures low.

Because botulism spores are commonly found in the Alaskan environment,[9-11] fermented foods may carry an irreducible risk of botulism. Changes in fermentation practices appear to favor *C botulinum* growth by providing warmer temperatures and longer incubation times. All reported fermentation times and temperatures in the Bristol Bay outbreaks were compatible with *C botulinum* toxin production. In the laboratory, botulism spores have been shown to be extremely sensitive to environmental conditions. For example, nonproteolytic type B spores produce toxin in 17 days at 5.6°C but in 85 days at 3.3°C.[12] Because the ambient temperature in Bristol Bay in July ranges from 5°C to 17°C, the holes dug into the cool permafrost and used as a fermentation chamber may have provided natural insulation from the summer heat, as do the icy river waters for the Athabascans.

Salt concentrations of 3% to 10% inhibit *C botulinum* growth. In southeast Asia, high salt concentrations protect against bacterial contamination during the fermentation of bean curd and fish,[13] and, in Japan, *izushi* fermentation is regulated by the salt concentration, incubation time, and temperature.[14] In Bristol Bay, however, salt is rarely used during fermentation.

Most of the Bristol Bay outbreaks were associated with fermented beaver tail, an uncommon, newly introduced fermented food. Thus far, outbreaks of botulism associated with beaver tail have been recognized only in Bristol Bay; it is not known whether fermented beaver tail is eaten in other regions. This cluster of outbreaks suggests that fermented beaver tail may be especially favorable to *C botulinum* growth and that the lack of traditional temperature and time guidelines may make its preparation especially risky.

Although a comprehensive survey of traditional food-eating habits in Bristol Bay was beyond the scope of this study, fermented food consumption appears to be decreasing. However, fermented foods remain popular among certain groups of Alaska Natives and are prized for their taste and as a symbol of native traditions. In this context, changes in preparation methods in Bristol Bay appear to have increased the risk of botulism by altering traditional time and temperature controls or the type of food itself. These changes may have shifted the delicate cultural and microbiologic balance protecting against this "hazard of the North."[5]

An educational campaign directed against fermentation in plastic bags appears to have discouraged this particularly hazardous practice in Bristol Bay. Recent outbreaks indicate the need to promote slow, cold temperature fermentation techniques and to avoid fermenting nontraditional foods, such as beaver tail. Because Alaska Natives are likely to continue consuming fermented foods, further educational efforts emphasizing these principles, along with the continued training of medical providers in the early recognition and treatment of botulism and the continued ability of public health agencies to investigate suspected outbreaks promptly, appear to be the most appropriate control measures to reduce the incidence and morbidity of botulism in Alaska Natives.

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Articles

HIV Antibody Seroprevalence Among Prisoners Entering the California Correctional System

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A cross-sectional blind study was conducted in the spring of 1988 to estimate the extent of human immunodeficiency virus (HIV) infection among inmates entering the California correctional system. Of the 6,834 inmates receiving entrance physical examinations during the study period, 6,179 (90.4%) had serum tested for the presence of HIV antibodies after routine blood work was completed and personal identifiers were removed. Seroprevalence was 2.5% (95% confidence interval, 2.1% to 3.0%) among the 5,372 men tested and 3.1% (95% confidence interval, 2.1% to 4.5%) among the 807 women tested. Seroprevalence was more than twice as high among men arrested in the San Francisco Bay Area as in those arrested elsewhere in the state. The regional differences in HIV seroprevalence observed among entering inmates mirror infection rates reported among intravenous drug users from the same regions.

(Singleton JA, Perkins CI, Trachtenberg AI, et al: HIV antibody seroprevalence among prisoners entering the California correctional system. West J Med 1990 Oct; 153:394-399)

The management of human immunodeficiency virus (HIV) infection and the prevention of HIV transmission in correctional facilities are among the most challenging problems now confronting prison officials. Many inmates have a preincarceration history of intravenous drug use, and both intravenous drug use and homosexual activity are known to occur in prisons.[1-4] Persons infected with HIV may therefore enter the prison system and transmit the virus within prison if there is no intervention.

Most states have initiated some form of HIV antibody testing among prisoners, with results to date indicating a wide range of HIV seroprevalence rates. Unlinked epidemiologic studies of HIV seroprevalence have been conducted in ten state correctional systems since 1985 (Table 1).[5-11] In these studies, HIV testing was done after all personal identifiers were removed from blood specimens drawn for other purposes. The seroprevalence of HIV was highest among inmates in New York (17% among men, 19% among women) and Maryland (7% among men, 15% among women). Other states reported HIV seroprevalence rates of 1.4% or less.

Unbiased estimates of HIV seroprevalence among inmates are also available from 13 states that have adopted a policy of mandatory HIV testing of incoming prisoners.[7] In the federal system, which tests 10% of new inmates and all inmates on release, seroprevalence was 2.0% among the 37,694 new and released prisoners tested from June 1987 through October 1988.[12] In Nevada the rate was 2.5% among 3,820 inmates tested in 1985.[5] Other jurisdictions with mass screening policies have reported seroprevalence rates of 1.5% or less and were typically states with a relatively low cumulative incidence of the acquired immunodeficiency syndrome (AIDS).[5] None of the five states with the highest cumulative AIDS incidence—New York, New Jersey, Florida, California, and Texas—currently screen all entering prison inmates for HIV infection on a mandatory basis.

The majority of state and federal correctional jurisdictions separately house inmates with confirmed diagnoses of AIDS. As of April 1988, at least ten states maintained separate housing for all inmates with known HIV infection, including those with asymptomatic infections.[7] California has followed this policy since 1985. As of July 1, 1988, the California Department of Corrections housed 176 inmates with known HIV infections (9 women and 167 men) at three facilities.*

To date, HIV testing in the California correctional system has been done only on consenting inmates when clinically indicated or upon inmate request. Because there currently are disincentives for prisoners to be voluntarily tested—that is, HIV seropositivity leads to segregated housing with AIDS patients and the loss of access to work programs—it is likely that the actual number of inmates with HIV infection is higher than the number presently identified by voluntary testing. State legislation mandating HIV antibody testing of all incoming prisoners in California has been proposed several times in recent years.

The California Department of Health Services, at the request of and in collaboration with the California Department of Corrections,† conducted a cross-sectional blind study during the late spring of 1988 to estimate HIV seroprevalence among incoming prisoners. Only existing demographic data and blood specimens drawn at routine medical examination on entrance to prison were used. The purpose of this study was to estimate the extent of HIV infection among entering inmates to assess future needs for housing and medical services and to provide data to assist in targeting AIDS prevention and risk-reduction activities.

*As of June 30, 1990, of the 525 inmates with known HIV infection, 95 were participating in three pilot projects to determine the feasibility of integrating inmates with HIV infection into the general prison population (Chris Cummings, California Department of Corrections, oral communication, August 13, 1990).

†Charles C. Jew, MA, Amnon Igra, PhD, Chris Cummings, and Nadim Khoury, MD, of the California Department of Corrections assisted in the planning and conduct of this study.

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
ELISA = enzyme-linked immunosorbent assay
HIV = human immunodeficiency virus
HIV-Ab = HIV antibody

Subjects and Methods

Population Studied

All incoming prisoners in California receive a routine physical examination shortly after arrival at the reception center, during which a blood specimen is obtained and tested for communicable diseases. The study population consisted of all prisoners scheduled to have venipuncture in association with physical examinations on entrance to the California correctional system from April 18, 1988, through May 13, 1988. Data collection from incoming women prisoners included an additional four-week period of May 23, 1988, through June 17, 1988.

Adult male prisoners are processed for entrance into the California correctional system at seven reception centers. Two reception centers receive prisoners arrested in the San Francisco Bay Area (San Francisco, Alameda, Contra Costa, Marin, San Mateo, Santa Clara, and Solano counties). Three reception centers receive prisoners arrested in southern California (Imperial, Inyo, Kern, Los Angeles, Orange, Riverside, San Bernardino, San Diego, San Luis Obispo, Santa Barbara, and Ventura counties). One reception center receives prisoners arrested in the remaining 40 counties located in central and northern California. The final reception center receives civil narcotics offenders from throughout the state, who receive drug treatment while incarcerated.

Within a region, the particular reception center to which a person is sent also depends on his or her commitment status. For this study, incoming male prisoners were classified either as parole violators returned to custody without a new term or as "new commitments." Approximately 80% of new commitments were not on parole when arrested for their admitting sentence, and 20% were parole violators with new terms.

Adult female prisoners enter the correctional system through three reception centers. One reception center receives all civil narcotics commitments, another receives parole violators from southern California and all new commitments, and the third receives parole violators arrested elsewhere in the state.

Data Collection

Data were collected using protocols approved by the California State Health and Welfare Agency Committee for the Protection of Human Subjects. Procedures were in accordance with California statutes that allow blind HIV antibody testing of serum collected for other purposes.[13] Consent is not required under these conditions if test results cannot be linked to a specific person. Following guidelines for blind HIV antibody testing developed by the Centers for Disease Control, new information cannot be collected from subjects solely for the purposes of the study. Information on risk behavior was therefore unavailable because it is not routinely obtained as part of the entrance examination.

Serum remaining after routine tests were done was placed in a separate vial, refrigerated, and sent to the HIV testing laboratory on a daily or weekly basis. Because of logistic and confidentiality concerns, vials were labeled only with the facility code and, for men, commitment status—parole violator or new commitment. Sex and geographic area where the crime was committed (San Francisco Bay Area, southern California, or north-central California) were facility-specific. Each reception center maintained a log of the number of physical examinations performed during the study period, which was compared with the number of specimens tested for the presence of HIV.

Laboratory Methods

All serum specimens were tested for the presence of human immunodeficiency virus antibodies (HIV-Ab) by the enzyme-linked immunosorbent assay (ELISA). Serum that was repeatedly reactive on ELISA was confirmed by Western blot. Western blots were interpreted according to criteria of the Association of State and Territorial Public Health Laboratory Directors and Centers for Disease Control.[14] Specimens that were indeterminate on Western blot were tested by immunofluorescence.[15]

Statistical Methods

Confidence intervals of 95% for HIV-Ab seroprevalence rates were calculated assuming binomial distributions for the number testing positive.[16] Seroprevalence rates in subgroups were compared using ratios of rates as estimates of

TABLE 1.—*Human Immunodeficiency Virus (HIV) Seroprevalence From Unlinked Epidemiologic Studies in State Correctional Systems*

State	*Year*	*Type of Prisoner*	*Number Tested*	*HIV Seropositive, %*	*Source*
Indiana	1987	New inmates	602	0.2	Hammett, 1988[5]
Iowa	1986	New inmates	859	0.0	Glass et al, 1988[6]
Maryland	1985	New male inmates	748	7.0	Hammett, 1988[5]
Maryland	1985	All new female inmates	39	15.4	Hammett, 1988[5]
Michigan	1986	New inmates	571	0.9	Hammett, 1988[5]
Mississippi	1987	New and current	1,000	1.4	*
New Mexico	1987	All new	501	0.8	Greenspan, 1988[7]*
New York	1988	New female inmates	450	18.9	Smith et al, 1989[8]
New York	1988	New male inmates	494	17.4	NY State Dept of Health, 1988[9]
Oregon	1987	All new inmates	977	1.2	Andrus, 1989[10]
Tennessee	1988-1989	All new inmates	1,490	0.9	†
Wisconsin	1986	New male inmates	997	0.3	Wisc Div of Health, 1988[11]

*From a survey of the 50 states and the Federal Bureau of Prisons conducted by the California Department of Corrections in July 1988 (Charles C. Jew, MA, written communication, August 2, 1988).
†Bernard H. Ellis, MA, MPH, AIDS Program, Bureau of Health Services, Tennessee Department of Health and Environment, written communication, May 20, 1989.

relative risk. Approximate 95% confidence limits were calculated for relative risks using the test-based method of Miettinen; for stratified comparisons relative risks were estimated by the method of maximum likelihood.[16]

Results

Sample Tested

During the study period, 6,834 inmates received intake physical examinations (Figure 1). Of these, 90.4% had serum tested for the presence of HIV-Ab. Of the 652 inmates whose serum was not tested, 425 were lost to testing because serum specimens were not saved or were lost or damaged. For the remaining 227 inmates, a blood specimen could not be drawn or an insufficient quantity was left for HIV-Ab testing after routine blood work. Western blots were not done on three specimens owing to laboratory error, and these are excluded from the study. Of the 6,179 serum specimens tested for HIV-Ab, 160 were positive (135 men and 25 women). The 14 specimens that were indeterminate on Western blot were negative on immunofluorescence and are considered negative for the purpose of analysis—included in the denominator.

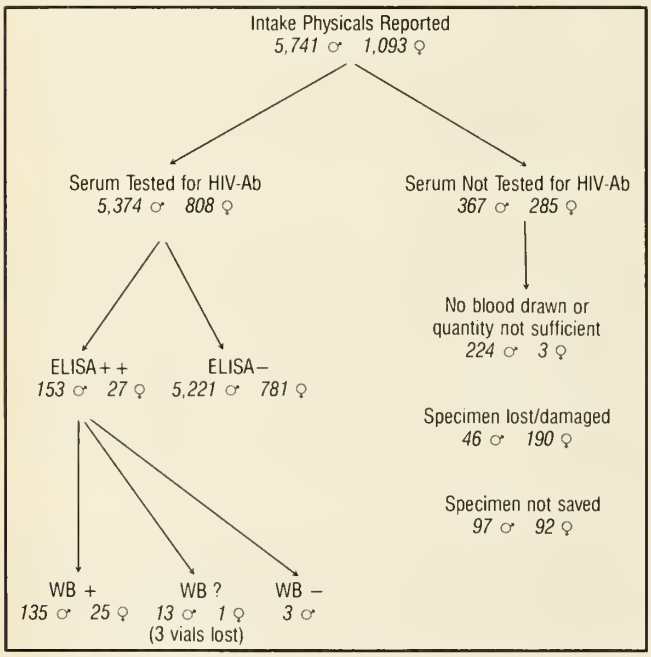

Figure 1.—During a 4-week period, human immunodeficiency virus seropositivity (HIV-Ab) of 6,834 prisoners entering the California correctional system was tested. Serum repeatedly positive on two enzyme-linked immunosorbent assays (ELISA) were confirmed by Western blot (WB). + = positive, ? = indeterminate, − = negative

Table 2 shows the demographic distribution of inmates entering the California correctional system during the study period. This distribution was not significantly different from that of inmates entering during the previous 12 months.

Seroprevalence

Table 3 presents HIV-Ab seroprevalence among the 6,179 inmates tested, by commitment status and sex. The overall seroprevalence among men was 2.5% (95% confidence limits, 2.1% to 3.0%); the rate among women was 3.1% (95% confidence limits, 2.1% to 4.5%). The overall rates for women and men were not significantly different (relative risk, 1.2; 95% confidence limits, 0.8 to 1.9).

Overall, 5.3% of men arrested in the San Francisco Bay Area were found to be HIV-Ab-positive (Table 4). Men arrested in this region were significantly more likely to be HIV seropositive than those from southern California (relative risk, 2.7; 95% confidence limits, 2.0 to 3.9) and elsewhere in north-central California (relative risk, 4.4; 95% confidence limits, 2.4 to 8.1). The difference in seroprevalence rates between those arrested in southern California (1.9%) and those arrested in northern or central California (1.2%) was not statistically significant.

Among men, parole violators had a somewhat higher seroprevalence rate than other groups tested (Table 3). This increase was not statistically significant, however, and comparison within geographic areas showed no consistent direction to the difference (Table 4).

Comment

This study is the largest blind seroepidemiologic survey so far reported of HIV prevalence among prisoners (Table 1). Several states with mandatory HIV screening have tested more prisoners but, with the exception of Nevada, reported low HIV seroprevalence and have a low incidence of AIDS.[5]

Although the inability to collect information on risk behavior in this blind study limits the interpretation of these data, they provide important information on the current scope of HIV infection in persons entering the California correctional system. This study indicates that the overall HIV-Ab seroprevalence among persons entering the California correctional system in the late spring of 1988 was approximately 2.6%. Specifically, male and female inmates appear to be equally likely to be infected on entrance to the correctional system, new civil narcotics offenders are no more likely to be infected than other new inmates, and the geographic area of arrest strongly affects the likelihood of being infected.

TABLE 2.—*Demographic Distribution of Inmates Entering the California Correctional System in April-May 1988**

	Men, % (n = 5,880)†				*Women, % (n = 1,123)*			
Age, yr	*White*	*Black*	*Hispanic*	*Other*	*White*	*Black*	*Hispanic*	*Other*
<25	5.9	10.3	8.2	1.0	4.8	5.9	5.8	1.1
25-29	8.2	12.1	8.4	1.1	9.6	9.7	8.8	1.1
30-34	6.2	9.0	5.4	0.6	9.3	9.8	6.3	2.1
35-39	3.9	5.3	2.8	0.5	6.9	4.5	3.4	1.7
>39	3.9	3.5	3.1	0.4	3.9	2.8	1.7	0.8
All	28.1	40.3	27.9	3.6	34.5	32.7	26.0	6.8

*Data were obtained from the California Offender Based Information system. This sample is representative of but does not exactly correspond to the sample of inmates tested for the human immunodeficiency virus (HIV) because there is a lag between the date of entry into the prison system and the date of the intake physical examination and because not all inmates scheduled for examinations during the study period were tested for HIV (see text).

†Totals do not add up to 100% due to rounding.

TABLE 3.—*Humon Immunodeficiency Virus Antibody (HIV-Ab) Seroprevolence Among Prisoners Entering the Colifornio Correctionol System**

Sex	Commitment Stotus	Persons Tested, No.	HIV-Ab Positive, No.	Prevolence, %	95% Confidence Intervol, %
♂	Parole violator (PV)	2,336	67	2.9	2.3-3.6
	New commitment (NC)	2,846	64	2.2	1.7-2.9
	Civil narcotics PV	83	1	1.2	0.0-6.5
	Civil narcotics NC	107	3	2.8	0.6-8.0
	All men	5,372	135	2.5	2.1-3.0
♀	PV and NC	679	23	3.4	2.3-5.0
	Civil narcotics PV and NC	128	2	1.6	0.4-5.5
	All women	807	25	3.1	2.1-4.5

*Study period was 4/18/88 to 5/13/88 for men and 4/18/88 to 5/13/88 and 5/23/88 to 6/17/88 for women. The dates of entry refer to dates of the receiving medical examination, which may be several days after official entry into the prison system.

This study provides no data on the seroprevalence of inmates already in the correctional system when the study began or on the transmission of HIV within the system. The application of these estimated rates to future entering inmates will depend on the course of HIV infection in the communities from which they come.

Selection Bias

Because an attempt was made to draw blood specimens from all incoming inmates, this study is not inherently limited by selection bias, as are studies that rely on volunteers or that target high-risk groups. Because not all of the incoming prisoners having physical examinations during the study period were actually tested, however, there is some potential for selection bias if the HIV-Ab seroprevalence rate among those tested substantially differed from the rate among those not tested. Of particular concern are those prisoners (224 men, 3 women) from whom no blood could be drawn or from whom so little blood could be drawn that an insufficient quantity of serum remained for HIV-Ab testing after routine blood work. Clinical experience indicates that such persons are more likely to be habitual intravenous drug users who have scarred or collapsed veins.

TABLE 4.—*Humon Immunodeficiency Virus Antibody (HIV-Ab) Seroprevolence Among Mole Prisoners Entering the Colifornio Correctionol System by Region of Arrest**

Region	Commitment Stotus†		
	Porole Violotor	New Commitment	Totol
San Francisco Bay Area			
% HIV-Ab-positive	6.5	4.1	5.3
(95% CI)	(4.7-9.0)	(2.8-6.2)	(4.1-6.9)
No. tested	536	530	1,066
Southern			
% HIV-Ab-positive	2.1	1.9	1.9
(95% CI)	(1.4-2.9)	(1.3-2.6)	(1.5-2.5)
No. tested	1,410	1,882	3,292
North-Central			
% HIV-Ab-positive	0.8	1.6	1.2
(95% CI)	(0.2-2.2)	(0.8-3.3)	(0.7-2.2)
No. tested	390	434	824

CI = confidence interval

*San Francisco Bay Area includes the counties of San Francisco, Alameda, Contra Costa, Marin, San Mateo, Santa Clara, and Solano; the southern region includes the counties of Imperial, Inyo, Kern, Los Angeles, Orange, Riverside, San Bernardino, San Diego, San Luis Obispo, Santa Barbara, and Ventura. The remaining counties of California form the north-central region.

†Civil narcotics commitments are excluded from this table; 8 were from the San Francisco Bay Area and 18 from north-central California.

In the unlikely event that all of these 224 men would have tested positive, the overall prevalence for male prisoners would be 6.4% compared with the 2.5% among those actually tested. If none would have tested positive, the prevalence would be reduced only to 2.4%. For women, the corresponding maximum and minimum values were 3.4% and 3.1%, respectively, compared with the 3.1% among those actually tested. The actual seroprevalence of entrants is likely to be somewhat higher than the seroprevalence of those tested but lower than the maximums calculated here. For example, assuming a 20% HIV seroprevalence in the untested high-risk group, the actual seroprevalence would be 3.2% for both men and women. Other HIV seroprevalence studies of prisoners have not addressed possible selection biases; whether these studies actually had problems in drawing sufficient serum from all entering inmates is unknown.

Intravenous Drug Use and Prisoners

There is a strong correlation between the HIV seroprevalence among prison populations and the seroprevalence among intravenous drug users entering treatment from the same areas. The HIV seroprevalence from unlinked and mandatory testing of prisoners in correctional systems[5,7,9,11] was plotted as a function of the average HIV seroprevalence among intravenous drug users from studies conducted in the corresponding states between 1984 and 1987 (Figure 2).[17] The high ecologic correlation observed is supported by results from the New York correctional system where the HIV seroprevalence among entering inmates with a known history of intravenous drug use was 44% compared with 7% among inmates who said they did not use drugs intravenously.[9] Some of the studies referenced above were conducted in prison populations; others were done in drug treatment centers, sexually transmitted disease clinics, and similar settings where self-selection may have upwardly biased the seroprevalence. The higher seroprevalence found in California, compared with the states mandatorily testing all incoming prisoners, is consistent with the higher cumulative incidence of AIDS in California.

The HIV seroprevalence among prisoners entering from the San Francisco Bay Area was found to be significantly higher than among those entering from the rest of the state. This may reflect that, as noted in Figure 2, intravenous drug users in the San Francisco Bay Area have a much higher HIV-Ab seroprevalence than those from Los Angeles and elsewhere in the state. The ecologic correlation between seroprevalence in intravenous drug users and inmates entering a correctional setting illustrates the important role

that prisons and jails could play in accessing these high-risk populations. Many such persons might not otherwise be reached by infection surveillance or control efforts.

Projections

Assuming the persons tested in this study represent a random sample of all entrants into the California correctional system over a longer period, the expected number of HIV-Ab-seropositive persons to be found if testing of all prisoners were required in the future can be estimated. Assuming a stable rate of infection in the population and based on a seroprevalence of 2.5% among men, an estimated 1,365 to 1,950 HIV-seropositive men may be identified among the 65,000 men who enter the system each year. If a 3.1% seroprevalence among women is assumed, there would be 105 to 225 seropositive women among the 5,000 women who enter California prisons each year. Because there is a lag between the time of infection and when HIV antibody levels are detectable, the total number of entering inmates with HIV infection is likely to be higher than these estimates. The total number of HIV-seropositive persons housed in the prison system at any given time would also depend on how long each HIV-seropositive inmate is incarcerated and on future increases in the number of entering inmates.

Policy Implications

These data point to both the opportunity and pressing need for reaching out-of-treatment drug users and others at risk in prisons with AIDS prevention and risk reduction messages, regardless of the testing or housing policies in the facility. Educational efforts should be tailored to the inmate population in consultation with medical and health education experts. This should be done on entry into the prison system, at frequent intervals while incarcerated, and also on release when the ability to engage in high-risk behaviors is increased. Effective educational efforts should help reduce HIV transmission within facilities, as well as in the communities in which the prisoners will live on release from the correctional system.

While most state and federal correctional systems segregate inmates diagnosed with AIDS, at least 10 of the 51 systems (including California) also segregate HIV-Ab-seropositive inmates.[7] Reasons given for segregating asymptomatic seropositive inmates include to protect seropositive inmates from hostile acts by other inmates, to minimize the transmission of HIV and the potential liability that may result if transmission did occur, and to facilitate delivery of the same programs other inmates receive while also attending to their special medical and psychosocial needs. California correctional officials plan to house asymptomatic HIV-infected inmates separately from those with clinical symptoms if funds become available to implement a modular housing concept that provides equivalent facilities for subgroups of inmates.

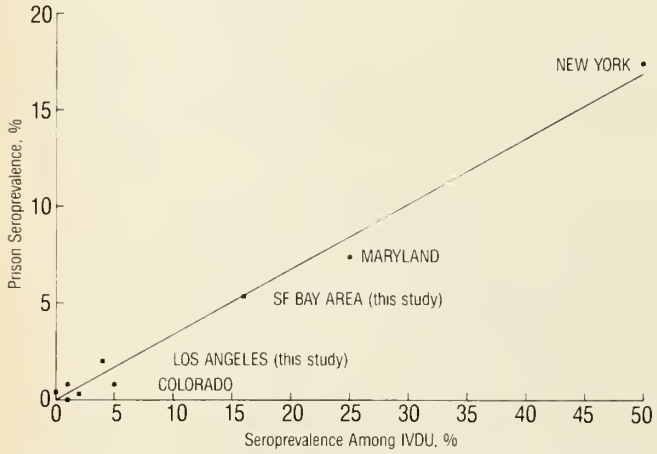

Figure 2.—The graph shows the seroprevalence of the human immunodeficiency virus antibody in prisoners in correctional systems compared with that of intravenous drug users (IVDU) from the corresponding states. The figures for Missouri, New Mexico, Washington, and Wisconsin occur near the origin. The plotted regression line has an adjusted R^2 of .99. From Hammett,[5] Greenspan,[7] NY State Dept of Health,[9] Wisconsin Division of Health,[11] and Centers for Disease Control.[17]

While there may be merit in the idea of separate housing for asymptomatic HIV-seropositive inmates, such a practice would require substantially increased resources to accommodate the large number of seropositive persons who would be identified under a mass testing program. The projections from this study indicate that separate housing for as many as 2,200 HIV-infected persons would need to be provided within the first year of mandatory testing. Consequently, it may be more difficult to provide separate but equal social, rehabilitational, and recreational facilities. The increased funding need may also decrease the quality of services and medical care provided to persons with AIDS because they would share facilities with a much larger group of seropositive persons.

If segregated seropositive prisoners are prevented from participating in work programs that lead to time off for good behavior, then increased costs for their medical care may accrue to the correctional medical system. Segregation can also result in a loss of confidentiality with labeling and stigmatizing that may inhibit rehabilitation. On release from prison, asymptomatic but publicly identified seropositive persons may suffer housing and employment discrimination. Segregating infected inmates may also provide a mixed message to inmates, their families, and the public at large once they are released into society and are no longer quarantined.

Even with mass screening and segregated housing, HIV transmission may still occur because some inmates tested soon after HIV infection will not test positive because of the lag between the time of infection and the time HIV antibody levels are detectable. This lag may be as long as six months and possibly longer.[18] Thus, the presumed uninfected population would have to be repeatedly tested to assure complete "capture" of seropositive persons. Segregating identified HIV-Ab-positive inmates will not obviate the need for intensive AIDS education and risk-reduction measures in the general prison population.

The assessment by prison officials of the potential for HIV transmission within correctional facilities plays a key role in policy decisions regarding HIV testing and the housing of HIV-seropositive persons. While sexual activity and intravenous drug use are prohibited among inmates, these activities are well known to occur within prisons. Indeed, there have been documented outbreaks of sexually transmitted diseases and hepatitis B in prison populations, although the rate of transmission has been found to be on the order of 1%.[19,20] Likewise, low but nonzero rates of HIV transmission have been documented in prison systems.[5,12,21,22] Transmission seems to depend, however, on the prevalence of HIV and the behaviors known to transmit it, and these factors may vary widely in different regions. Follow-up studies of a cohort of entering and current inmates would provide the most definitive information regarding the transmission of HIV within correctional sys-

tems. The random assignment of some physically separate prison cohorts to have condoms and bleach made available to them might also provide valuable information on the prevention of HIV transmission in the correctional setting and should be considered. Studies providing reliable information in this regard would be useful in making policy decisions and in further targeting prevention efforts.

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Articles

Immunizing California's Children
Effects of Current Policies on Immunization Levels

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Data collected by the Immunization Unit of the California Department of Health Services from 1979 to 1987 were analyzed to determine the effects of changes in state policy on the immunization levels of children in California. By December 1986, 90% of all children entering kindergarten in California were adequately immunized, representing a 15% increase from 1979. Although California has shown substantial improvements, it still lags behind the national weighted average. Even with high levels of immunization at kindergarten entry, many toddlers of 7 months and 2 years old remain inadequately immunized. Children immunized solely in the private sector were more adequately immunized than those served by public health clinics; the public-private difference for infants aged 7 months was nearly twofold.

(Scheiber M, Halfon N: Immunizing California's children—Effects of current policies on immunization levels. West J Med 1990 Oct; 153:400-405)

Immunizations against infectious diseases have had a remarkable effect on the profile of childhood morbidity and mortality and, for most children, have eliminated the threat of many childhood illnesses. So important are immunization programs that levels of childhood immunizations have often served as a general indicator of the health status of a given population. Moreover, these programs have been shown to be cost-effective, with measles vaccination, for example, resulting in an estimated net savings of $5.1 billion during the first 20 years of its licensure in the United States (1963 to 1982).[1] In addition, even given the problem of occasional adverse reactions to pertussis vaccinations, the ratio of overall costs to a community without a DPT [diphtheria and tetanus toxoids with pertussis vaccine] immunization program to those with a program were estimated at 5.7:1.[2,3]

Despite the remarkable progress made in immunizing children, vaccine-preventable illness continues to occur, certain segments of the child population remain underimmunized, and vaccine-related complications continue to occur. The purpose of this study is to assess current levels of immunization for children in California and to determine the effectiveness of policies aimed at improving the efficacy of immunization programs.

In 1977 a federal effort was made to increase immunization levels in the United States. The goal was to raise immunization levels in American children for the common vaccine-preventable diseases to more than 90% by 1979. This goal was achieved with success in school-aged children, and two new goals for 1990 were established in December 1980 by the Public Health Service: to raise national immunization levels in toddlers to 90% by age 2 years and to raise the immunization levels of children in day-care centers and schools (grades K through 12) to 95%.

Vaccine-preventable illnesses continue to plague children in the United States, however. In the time span January 1, 1978, through June 30, 1986, more than 17,000 cases of vaccine-preventable infectious diseases were reported in the state of California alone (California Department of Health Services [CDHS] data). In 1982 and 1983, of reported pertussis cases in the US in children aged 3 months to 6 years, 68% occurred in inadequately immunized children.[4] National estimates indicate that susceptibility rates to measles or rubella may be as high as 20% in our colleges and universities. There were major measles outbreaks in California in Los Angeles County in 1984, Riverside County in 1985, and San Bernardino and Sonoma counties in 1986 (CDHS data).

More recently in California during a measles outbreak between April 1 and June 30, 1990, measles was reported to occur in 1,799 persons aged 16 months to 33 years. Of these cases, 70.6% occurred in persons without documented adequate immunization after 12 months of age (CDHS data).

Statutory initiatives have had a major influence on the levels of immunization by mandating certain immunizations for school entry. Senate Bill 942 was passed in California in 1977 to provide a comprehensive, compulsory school immunization law. This bill clarified much of the confusion surrounding vaccine requirements for school registration and instituted uniform vaccine requirements. It repealed existing immunization laws and substituted one uniform law for all required immunizations. It also standardized school immunization records, entrance requirements, and sanctions against unimmunized students. The impact of this legislation is reflected in the incidence of selected vaccine-preventable diseases in California for 1977 and 1985, showing that this policy has brought about a decrease in the incidence of these diseases (Figure 1).

Even more stringent requirements implemented in 1986 increased accountability by requiring children entering California schools or state-licensed child day-care centers to provide a written immunization record for each required vaccine dose from a health care professional, including specifying the year and month of vaccine administration.

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This work was partially supported by the James Irvine Foundation and the Harris Trust of the Institute of Governmental Studies, University of California, Berkeley.

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ABBREVIATIONS USED IN TEXT

CDHS = California Department of Health Services
CSIR = California School Immunization Record
DPT = diphtheria and tetanus toxoids and pertussis vaccine
OPV = oral [attenuated] poliovirus vaccine

Before this change, guardians without written immunization records for their children had the option of filling out and signing the California School Immunization Record.

This study reviews and analyzes data collected by the CDHS Immunization Unit to determine current levels of immunizations, trends in those levels of immunizations, the factors associated with those trends, and policy alternatives that could prove useful in meeting identified shortfalls.

Methods

Data from the CDHS Immunization Unit from 1979 to 1987 were analyzed. These data were generated from two annually state-administered surveillance systems: the Selective Review and the Kindergarten Survey.

Selective Review

The selective reviews are extensive surveys conducted by the Immunization Unit to review and establish the validity of data on the immunization status of children in California's schools and day-care centers.* The purpose of the reviews is to evaluate the effectiveness of the follow-up of conditionally admitted students, to verify the data obtained on the annual Kindergarten Survey (school entry data), and to conduct retrospective studies of immunization levels of children at various age checkpoints.

The selective reviews are conducted at approximately 280 schools in California, which constitutes a sample size to achieve 95% confidence intervals that would allow the estimation of the percentage of unimmunized children to be in the range of 10%. Schools are randomly selected, but if that school has already participated in a previous selective review, it is replaced by another school selected at random. The CDHS has accepted the small loss in validity generated by this selection system because of the advantage of increased quality control of record-keeping that generally results from a school's participation in a selective review. Two children at each school are randomly selected and their California School Immunization Records (CSIRs) are reviewed by CDHS staff members. Two studies were done, one in Los Angeles County and the other at the state level, that measured the accuracy of the CSIR as compared with parents' documented records. Both studies indicated that parents' written immunization records matched comparably with the CSIRs within a margin of 5% error (CDHS data). Since the initial school review in 1981 the state has added a similar review of child care centers, reviewing approximately 210 to 215 centers each year.

*The CDHS defines a day-care center as any facility located outside of a private home, usually with more than 12 children, and does not confine its data collection to those institutions licensed by the Department of Social Services.

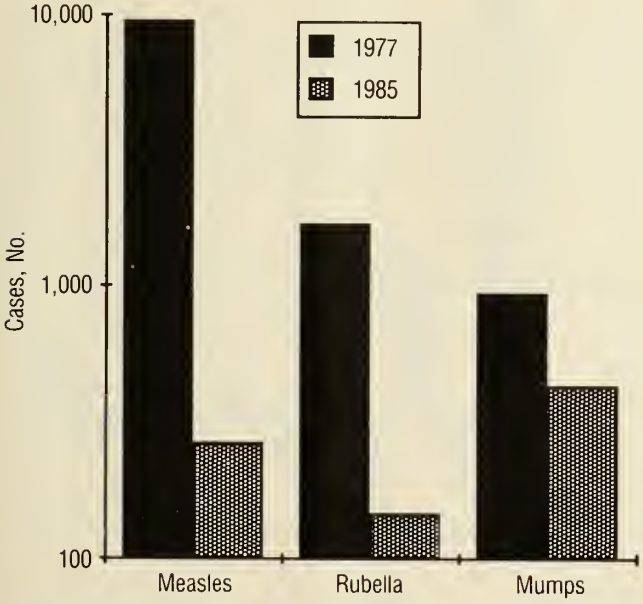

Figure 1.—The graph shows the number of cases of selected vaccine-preventable illnesses in California in 1977 and 1985 (compiled from California Department of Health Services data).

Kindergarten Survey

Kindergarten surveys were done by schools on a voluntary basis between 1974 and 1977 and were mandated after 1978. This law requires that one employee from each school with kindergarten grades compile all the CSIRs for the kindergarten children and tally the number and percentages of children up-to-date for each of the required vaccinations.

Results

Immunization Levels in California School Children

The kindergarten survey completed on January 22, 1987, shows that in 1986, 90.12% of all children beginning kindergarten (public and private schools combined) in California had school records indicating that they had received all the immunizations required for school registration. Table 1 shows the vaccine requirements for kindergarten effective September 1986. The percentage of children who are adequately immunized at the start of kindergarten has increased about 15% since 1979 (Figure 2). Nevertheless, California still falls slightly below the national weighted average that the Centers for Disease Control report for percentages of school children who have completed all state-required vaccinations (Figure 3).

School Compliance With Official Policy

As would be expected, as immunization levels rise, the total percentage of students with conditional admissions to kindergarten (those needing one or more immunizations

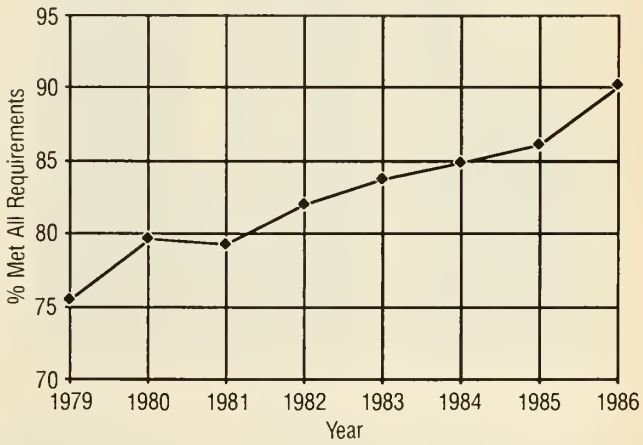

Figure 2.—The percentage of students is shown who enter kindergarten in California meeting all legal vaccine requirements at the time of school entry, by year, from 1979 to 1986 (compiled from California Department of Health Services data).

TABLE 1.—*School Entry Vaccine Requirements for the State of California, Effective September 1986*

Vaccine	*Minimum Doses Required*	*Additional Dose Requirements*
Polio (trivalent OPV)	3*	1 more dose if last was before 2nd birthday
Diphtheria, tetanus, and pertussis (DTP)		
Age 6 yr or younger—pertussis required		
DTP or any combination of DTP with DT or Td	4, but . . .	1 more dose if last was before 2nd birthday
Age 7 yr or older—pertussis not required		
Td, DT, or DTP or any combination	3, but . . .	1 more Td dose if last was before 2nd birthday
Measles, rubella, mumps†	1 each, but . . .	1 more dose of any given before the first birthday
Can be given separately or together		

DT = diphtheria and tetanus toxoids, adsorbed, pediatric; Td = adult tetanus toxoid (full dose) and diphtheria toxoid (reduced dose)

*If inactivated poliovirus (IPV) or a combination of oral, attenuated poliovirus (OPV) and IPV was given, at least 4 doses are required. One more dose is required if the last dose was given before the second birthday.

†Mumps immunization is not required for pupils 7 years of age and older.

who were allowed to attend classes for the grace period) has been declining (Figure 4). The 1987 Selective Review indicated that 85% of public kindergartens and 75% of private kindergartens were strictly and completely enforcing the new school entry regulations at the time of the survey. In the day-care centers, the new regulations are being enforced by 88.5% of Head Start programs, 74.3% of public day-care centers, and 64.1% of private day-care centers.

Between the kindergarten surveys, compiled at the time school starts, and the selective reviews conducted six months later, the schools have time to enforce the regulations and ensure that all conditionally admitted students receive the immunizations they are missing. Private schools and public schools have different rates of compliance to the requirements. Public schools more rigorously follow up on conditionally admitted students (Figure 5).

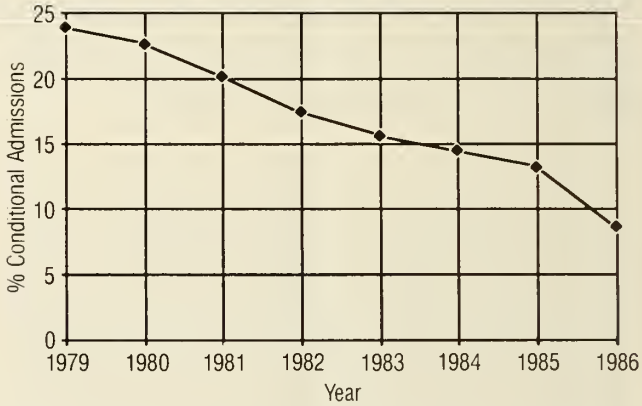

Figure 4.—The percentage of students is shown who entered kindergarten in California by year from 1979 to 1986 whose vaccine status was classified as conditional at the time of school entry (compiled from California Department of Health Services data).

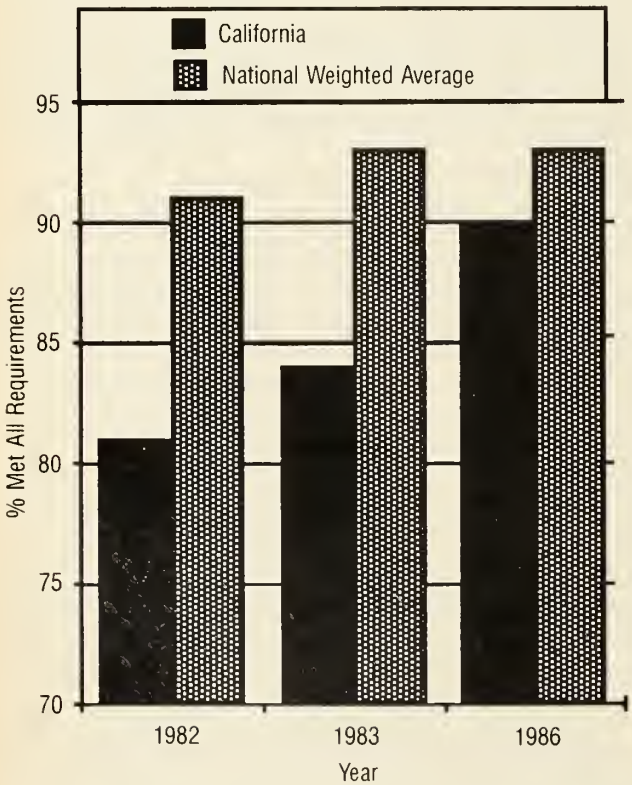

Figure 3.—The percentage of students is shown who enter kindergarten in California meeting all legal vaccine requirements at time of school entry compared with the national weighted average by year for 1982, 1983, and 1986 (compiled from data from the California Department of Health Services and the Centers for Disease Control).

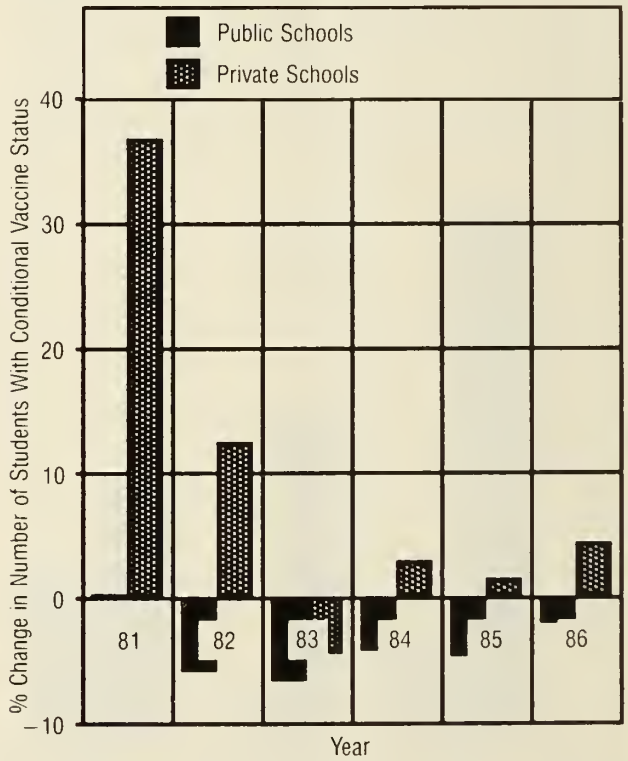

Figure 5.—The percentage change is shown for the number of students with conditional vaccine status between school entry and selective review in public and private schools in California by year, from 1981 to 1986 (compiled from California Department of Health Services data).

Underimmunized Segments of the Population

By retrospectively examining individual immunization records during the selective reviews, we were able to estimate immunization levels for groups of children at different ages before school entry. Children aged 2 years and 7-month-old children are particularly underimmunized segments of the California population. While the percentage of these children who are adequately immunized has been increasing with time (Figure 6), the immunization levels for these two groups are both considerably lower ($P < .001$) than the levels for 1-year-olds and kindergartners.

During the 1987 selective school review, the California Immunization Unit conducted a special retrospective survey to identify the source of immunization of California children and to compare school immunization records with parental records kept at home. Based on the school immunization records and parental responses, children in the survey were immunized by the following types of medical provider: private physician, 67.2%; public clinic, 15.6%; public and private combination, 16.7%; and military, 0.5%. Further analysis revealed that health maintenance organizations are the sole medical source for 10.2% of the children, and another 7% used a combination of health maintenance organizations and other providers to obtain their immunizations.[5]

At each age checkpoint, children who received their immunizations solely in the private sector were more adequately immunized than children served by public health clinics (Figure 7).[5] At certain ages, the discrepancy is significant. For instance, at 7 months of age only 32% of children using public clinics were adequately immunized, whereas 63% of those using private physicians were up-to-date.

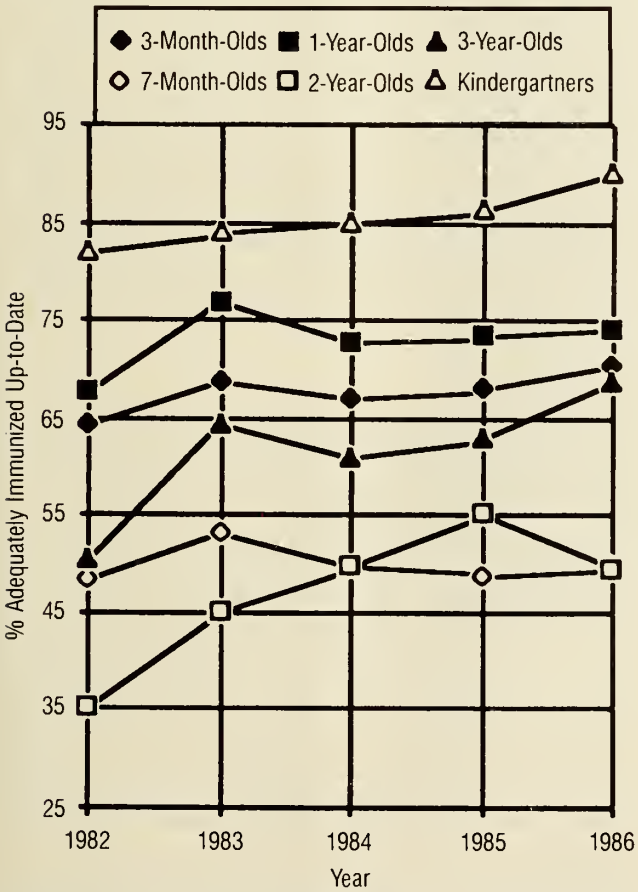

Figure 6.—The graph shows the percentage of California children whose vaccine antigens are all up-to-date, by age group and year from 1982 to 1986 (compiled from California Department of Health Services data).

Discussion

The data presented here show that while immunization levels in California children are still slightly below the national average, they are improving. Recent legislative changes in California have clarified vaccine requirements and public health implementation at the school level. Public schools are complying with the new regulations to a greater extent than are private schools and have a lower percentage of students with conditional vaccine status at the time of both the kindergarten survey and the selective reviews. Young children, especially 7-month-old and 2-year-old children, have disturbingly low immunization levels. Furthermore, this "toddler gap" is nearly twice as great for children dependent on public clinics for their vaccinations as for children who receive their immunizations in the private sector.

As immunization levels increase in California, they are approaching the national average. Several considerations may explain California's apparent shortcomings. Vaccine requirements in California are more rigorous than in many other states. For instance, during the 1985-1986 school year, vaccination against mumps, required for grades K through 12 in California, was not required for any grade in 17 states and was required of new entrants only or only for grades K through 6 or lower in 17 states. Also, most states report kindergartners with a total of four doses of DTP and three doses of oral, attenuated poliovirus vaccine (OPV) as adequately immunized, whereas California reports these children as inadequately immunized if all doses were received before the second birthday. Furthermore, the new California laws require stricter documentation than other states for counting a child's immunizations up-to-date.

Part of the real gap between California's and the national coverage may be explained by the sheer magnitude of the responsibilities facing California public health professionals. California is responsible for immunizing a large population of children, many of whom are immigrants. Approximately 433,334 infants are born each year in California, a figure that represents about an eighth of the children

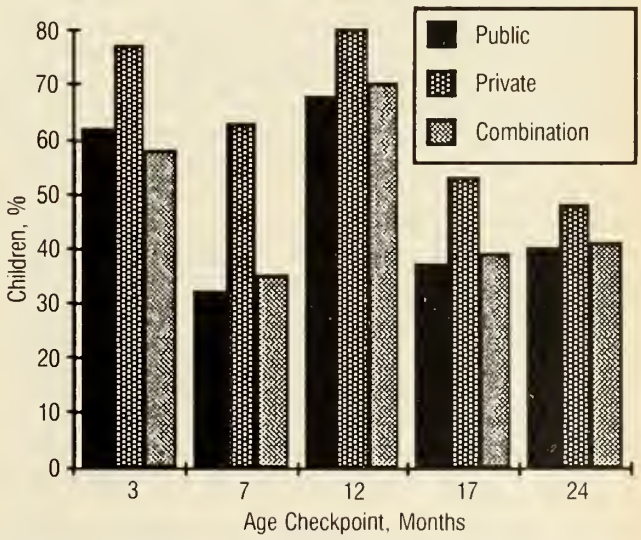

Figure 7.—The graph shows the percentage of children adequately immunized by source of immunizations at different age checkpoints. Data are from the California retrospective survey of kindergarten children, spring 1987, based on 188 (93%) school records and parental responses (California Department of Health Services data).

born in the United States and more than the combination of births occurring annually in 19 states and the District of Columbia (California Department of Finance, Population Research Unit, Sacramento, July 1, 1985).

The new school entry regulations seem to be having some effect on the immunization levels of school children. In the years 1979 and 1986, the largest yearly increases occurred in immunization levels and coincided with the passage of Senate Bill 942 and the most recent legislative changes. The 1986 data also represented the biggest yearly decrease during the eight-year period 1979 to 1986 in the percentage of children starting school whose immunizations were not up-to-date for all antigens. It is anticipated that when the data become available, the fall in conditional admissions will be seen to have been even more dramatic for the school year beginning September 1987 because a considerable number of children had already registered for the 1986-1987 school year by the time the new regulations went into effect in March 1986.

While the 1986 amendments, as indicated, did manage to decrease the number of students conditionally admitted, the new regulations did not have a large impact on the follow-up of those students who were illegally or mistakenly admitted. The increase in the number of students in public schools whose immunization status was classified as conditional at selective review can occur by either of two means: through the discovery at the selective review that children who the school had admitted as up-to-date were really misclassified and were missing one or more immunizations, or through admitting more students on a conditional basis. The Immunization Unit of the CDHS finds that the misclassification of children's immunization status at the initial school survey may be a likely cause for the increase. Selective reviews show that many students who had received measles, mumps, and rubella vaccinations before their first birthday or all of their DPT/DT[diphtheria and tetanus toxoids]/OPV immunizations before their second birthday were mistakenly classified as unconditional. This is a reassuring finding because most of these children are not totally lacking immunity. Rather, the boosters provide future protection against waning immunity or remove the small probability that the first series of shots did not provide adequate immunity.

Financial incentives may help to explain some of the differences noted in the data between public and private schools. The fact that private schools and day-care centers are less strictly enforcing the new vaccine laws than are public schools may reflect the fact that private institutions more completely depend on full enrollment for continued viability.

The toddler gap in immunizations has been a major health problem in California. Its consequences are illustrated by a sampling of disease statistics. In 1979 in California, there were 122 reported cases of pertussis. Of these cases, 92 (75%) occurred in children younger than 5 years. Infants younger than 1 year represented 54% of cases.[6] In 1980 California had 147 reported pertussis cases, 78% of which occurred in children younger than 5 and 54% in infants younger than 1.[7] California had 9,477 measles cases reported in 1977, 18% of which occurred in children younger than 5 years.[8]

For inadequately immunized toddlers, the disparity between those children receiving their immunizations from private physicians and those immunized in the public clinics is striking. Similar discrepancies have been documented in other states and have been likened to outbreaks of measles in public-sector immunized children.[9] Children cared for in public clinics include those covered by Medi-Cal (California's Medicaid) and those children presumed to have no health insurance. In 1986, despite the fact that California has one of the most generous state Medicaid systems, 23% of children in California had no public or private insurance coverage. This situation is especially tragic when California's version of the federal Early Periodic Screening, Diagnosis and Treatment Program—the Child Health and Disability Prevention Program—provides a financial mechanism for all children 29 months of age or younger who live in families with incomes as high as 200% of the poverty level to receive proper immunizations and health care maintenance services. Yet, the program currently reaches less than 30% of those eligible.[10]

Why does the great discrepancy between the public and private sectors exist, and why is the Child Health and Disability Prevention Program so underused? Children from low-income families who use public clinics for immunizations and health care frequently encounter numerous barriers to health care access. Many public clinics have episodic and irregular hours, long waiting times, insufficient outreach, and poor monitoring. For many of the immigrant families using public clinics, even a small degree of official government contact can be inhibiting. For other families living in poverty, or near poverty, other events and demands can outweigh the timely completion of immunization schedules.

In 1986 the CDHS implemented programs to try to reduce this toddler gap and ensure that 90% or more of the children born in California each year are up-to-date for all antigens by age 2. These programs included increased emphasis on hospital-based education for new mothers, involving the Women, Infants, and Children Supplemental Food Program and other organizations to include immunization as a criterion for receiving other infant and toddler care and improving education by health care providers with such items as the "Date Next Immunization Due" stickers for the outside jackets of a child's immunization record. Also, the expansion of eligibility for the Child Health and Disability Prevention Program in recent years has been specifically targeted at children up to age 29 months, thereby possibly addressing the specific immunization needs of infants and toddlers.

Policy Implications

Efforts must be strengthened and continued in order to raise toddler immunization levels to an acceptable level. One way of effecting increased levels of immunization in toddlers would be through health education efforts. A successful media campaign could alert parents to the danger of vaccine-preventable infectious diseases. Such an effort was successful in Great Britain at the height of a pertussis epidemic in 1982 and has been a major strategic intervention of other successful preventive health programs. Extensive national campaigns have produced positive public health behavioral changes in many areas, such as smoking cessation and dental hygiene.[11,12] Even longer term increases in immunization levels might be achieved by including vaccine information sessions in health education programs at the school level or by including vaccine education in prenatal programs.

Educational efforts must be coupled with improved outreach and access. California's Child Health and Disability Prevention Program is the best mechanism for providing access to needed preventive health services including im-

munizations. Because of fiscal constraints, this program currently reaches only a fraction of those children eligible for services. Additional funds provided by California State Proposition 99, the cigarette tax, will be allocated to the program in 1989-1990. It is hoped that the infusion of additional funds will provide the means to increase access for uninsured and underinsured children and improve the rates of immunization.

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Exploratory Surgery

Even asleep you feel the cutting
edge. A fissure lengthens,
swallows boulders, uprooted trees,

exposes the cavernous white
of deeply buried bone. Oddly
angled buildings work

into your dreams; trucks roll
across the rubble of the bed.
You rise, toppling cabinets, sinks,

the pillars of ancient tombs.
Lightheaded still, your shaking
goes on and on. Meat spoils

in the aftermath. Crumbled walls
prevent your body from being
recovered. In time

even the bleeding stops.
Eventually the ground re-seeds.
Water mains are clamped,

tucked back into place.
One day you dress.
Pansies bloom. Your face

is mapped with hairline cracks.
You examine yourself
for scars.

MARILEE RICHARDS
Alameda, California

Conferences and Reviews

Medical Management of Congestive Heart Failure

ANDREW E. ARAI, MD, *and* BARRY H. GREENBERG, MD, *Portland*

The syndrome of congestive heart failure can result from a variety of cardiac disorders of which left ventricular dysfunction is the most common. The clinical presentation is determined by the interaction between cardiac dysfunction and a series of compensatory mechanisms that are activated throughout the body. Therapy for this disorder is best approached through an understanding of this complex relationship and an appreciation for the influence of preload, afterload, and contractility on cardiac performance. Recent important advances in therapy include the use of combined diuretic therapy, a better understanding of the value of the digitalis glycosides, and evidence that angiotensin-converting enzyme (ACE) inhibitors can relieve symptoms and prolong life. More intensive therapy earlier in the course of congestive heart failure appears to have some clinical benefit. The use of ACE inhibitors during this phase may delay progression of the underlying left ventricular dysfunction. Future therapy will be influenced by the results of ongoing trials that are testing both new agents and expanded indications for drugs that are currently available.

(Arai AE, Greenberg BH: Medical management of congestive heart failure. West J Med 1990 Oct; 153:406-414)

Congestive heart failure (CHF) is a complex clinical syndrome resulting from cardiac dysfunction and the ensuing pathophysiologic responses that occur throughout the body. Defined clinically, it encompasses signs and symptoms resulting from low cardiac output and from pulmonary and systemic congestion. The syndrome of CHF can develop as an expression of a wide variety of disease processes that lead to cardiac dysfunction. For example, CHF can be right- or left-sided, acute or chronic, or due to abnormalities in diastolic or systolic function. Although conditions that affect myocardial function, such as coronary artery disease or idiopathic dilated cardiomyopathy, are the most common cause of CHF, valvular lesions, structural abnormalities, and pericardial disease can all give rise to this syndrome. In approaching patients with CHF, it is essential to determine the underlying cause because therapy is highly dependent on etiology.

In this review we focus on the therapy for chronic CHF due to left ventricular myocardial dysfunction. After a brief description of the epidemiology of CHF and an overview of pathophysiologic mechanisms, the discussion focuses on the pharmacologic agents that are currently available for treatment. Recent information that has influenced our approach is stressed, and practical guidelines for the initiation of therapy are considered. We conclude with a few brief thoughts about future directions in the treatment of this disorder.

Epidemiology

Congestive heart failure is a common condition with a prevalence of between 2 and 3 million persons and approximately 400,000 new cases each year in the United States.[1] The incidence of CHF appears to be steadily increasing—a problem brought on by the higher incidence of this condition in the elderly and the general aging of the population. The development of CHF has a dramatic effect on prognosis. In the Framingham study, the respective one- and five-year survival rates after the syndrome developed were 79% and 38%, respectively, for men and 86% and 57% for women.[2] In other studies that evaluated the natural history of more severe CHF, one-year survival has ranged between 34% and 70%.[3-7] Discrepancies in survival data between studies are likely due to differences in patient selection.

Determinants of Systolic Function

To treat CHF, it is essential to understand how various factors influence overall cardiac performance. The three major determinants of systolic pump function are preload, afterload, and myocardial contractility. The clinical definition of left ventricular (LV) preload is derived from characteristics of individual muscle fibers. The amount of tension a muscle fiber develops after activation increases (up to a limit) as the prestimulus muscle length is increased. The left ventricle is a three-dimensional array of cardiac muscle fibers, and it exhibits similar increases in peak tension development as it is distended to larger volumes during diastole. Thus, preload reflects the degree to which myocardial fibers are stretched during diastole.

Variables that can be measured to assess preload include LV diastolic volume and LV end-diastolic pressure. The latter is commonly estimated by the pulmonary capillary wedge pressure. The curvilinear relationship between ventricular filling volume and pressure is illustrated in Figure 1. Although LV preload is best represented by the end-diastolic volume, this measurement is more difficult to obtain than pressure measurements, which can be continuously monitored at the bedside.

The LV function curve depicted in Figure 2 shows the relationship between preload (filling pressure) and systolic LV performance (stroke volume). At low or normal filling pressures, small increases in preload result in large increases in stroke volume. As the curve begins to flatten, further increases in preload have progressively less of an effect on stroke volume. Elevated filling pressures, however, are an important factor in the development of congestive symptoms because they ultimately lead to an increase in pulmonary and systemic capillary hydrostatic pressure.

Afterload describes the forces that resist shortening of the myocardial fibers. There is an inverse relationship between afterload and ventricular emptying such that high

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ABBREVIATIONS USED IN TEXT

ACE = angiotensin-converting enzyme
BUN = blood urea nitrogen
CHF = congestive heart failure
LV = left ventricular
NYHA = New York Heart Association

levels of afterload tend to impair left ventricular emptying and reduce the stroke volume. As shown in Figure 2, an increase in the afterload will shift the LV function curve downwards so that there is a reduction in the stroke volume at any given level of preload. Afterload is best represented by LV systolic wall stress, but this variable is not readily measurable in most clinical settings. Systemic vascular resistance, which is derived from hemodynamic variables measured at the bedside, can be used to approximate the afterload.

Contractility describes the maximal rate of fiber shortening and tension development that the myocardial fibers could achieve in an idealized experiment requiring no work. Changes in systolic function that occur independent of changes in preload or afterload are defined as changes in contractility. Various positive inotropic agents including catecholamines, the digitalis glycosides, and phosphodiesterase inhibitors can increase contractility. Negative inotropic agents like alcohol, many antiarrhythmic agents, β-blockers, and calcium channel blockers can decrease contractility. Positive inotropic agents shift the LV function curve upward, and negative inotropic agents have the opposite effect.

Diastolic Dysfunction as a Cause of CHF

In addition to LV systolic dysfunction, abnormalities in diastolic function may cause or contribute to the development of congestive heart failure. Although a recent series suggested that as many as 36% of patients with CHF may have had diastolic abnormalities as the cause of the syndrome,[8] in our clinical experience the prevalence is probably in the range of 5% to 10%.

The mechanism by which abnormalities in LV diastolic function may lead to signs and symptoms of CHF is illustrated in Figure 1. Normally, relatively small changes in pressure develop in the left ventricle as it fills to a volume that is adequate to maintain cardiac output. At higher volumes the relationship steepens so that there are greater increases in filling pressure for each increment in volume. Thus, in a normal ventricle, symptoms of congestion are likely to occur only when volume overload is severe. A variety of conditions, however—summarized in Table 1—can alter the diastolic characteristics of the left ventricle so that it is stiffer or less compliant. This will have the effect of shifting the pressure-volume relationship upward and to the left. When this occurs, a given increment in diastolic volume will result in a greater increase in filling pressure than would be seen in a normal or more compliant chamber.

TABLE 1.—*Differential Diagnosis of Congestive Heart Failure in Patients With Normal Left Ventricular Systolic Function*

Diastolic dysfunction
Hypertrophic cardiomyopathy
Hypertensive cardiomyopathy
Restrictive cardiomyopathy
Idiopathic
Amyloidosis
Hemochromatosis
Ischemia
Old age?
Isolated right heart failure
Cor pulmonale
Right ventricular infarction
Pulmonary embolism
Pulmonary hypertension
Valvular disease
Aortic stenosis
Aortic regurgitation
Mitral stenosis
Mitral regurgitation
Pericardial disease
High-output failure

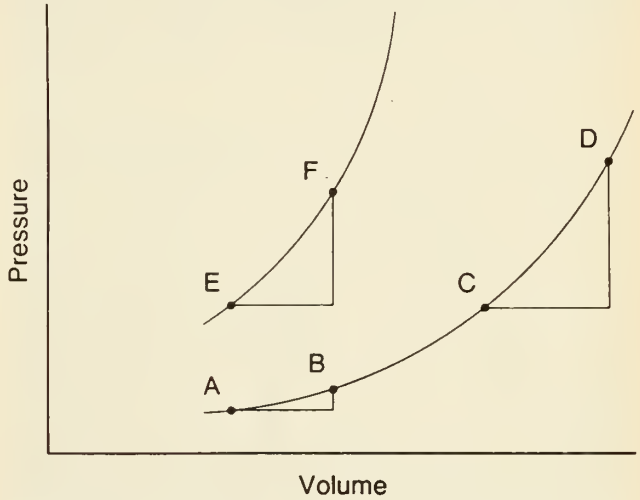

Figure 1.—The pressure-volume relationship of the ventricle during diastole is curvilinear. When a normal ventricle is relatively empty, increases in volume are accommodated with smaller changes in pressure (A to B) than occur when the ventricle is already distended (C to D). Abnormalities of diastolic function may decrease compliance such that the pressure-volume relationship is displaced upward from normal. In this case, an increase in volume comparable to the first example (A to B) results in a larger increase in pressure (E to F).

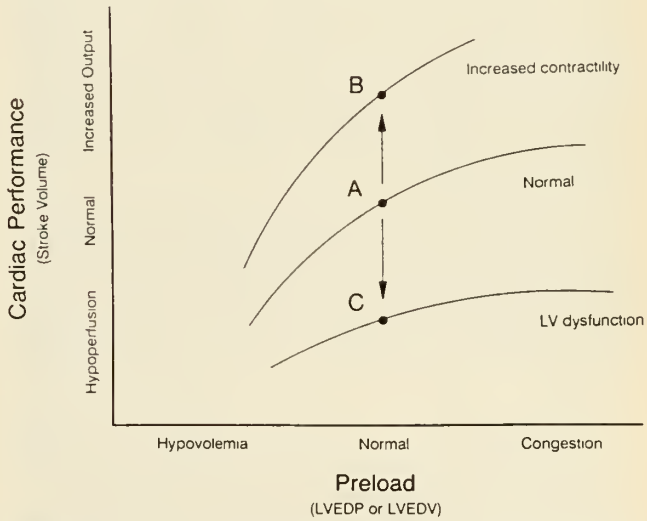

Figure 2.—The left ventricular (LV) function (Frank-Starling) curve describes the relationship between systolic cardiac performance (stroke volume) and preload, measured as the left ventricular end-diastolic volume (LVEDV) or end-diastolic pressure (LVEDP). Factors that increase contractility or reduce afterload displace the LV function curve upward so that at a given filling pressure the stroke volume is increased (A to B). Decreased contractility or increased afterload shifts the curve downward, resulting in smaller stroke volumes at given filling pressures (A to C).

Therefore, even if systolic function remains unimpaired, diastolic abnormalities alone could result in the development of pulmonary congestion. Increased LV stiffness may also impair diastolic filling to the extent that the stroke volume is reduced. Because a forceful atrial contraction is required to fill the stiff ventricle and to decompress the pulmonary venous circuit, the development of atrial fibrillation can lead to a sudden and dramatic deterioration in cardiac performance in patients with diastolic dysfunction.

Pathophysiologic Compensations Invoked by CHF

The heart and the circulatory system have a great capacity to respond to changes in myocardial function. Overall cardiac performance is determined by both the extent of myocardial dysfunction and the subsequent activation of compensatory mechanisms. Unfortunately, there is evidence that many of the compensatory responses have adverse effects on cardiac function, particularly when they are maintained over time.[9]

Reflex stimulation of the sympathetic nervous system plays an important role in the compensatory response to a decrease in cardiac output. Catecholamines enhance cardiac output by increasing the heart rate and the force of contraction. Catecholamine-induced constriction of arterial resistance and venous capacitance vessels helps to maintain the perfusion pressure and cardiac output by increasing systemic vascular resistance and by enhancing the return of blood to the heart. The negative consequences of these adaptations include a diminished LV contractile performance from the increased afterload and congestive symptoms from elevated filling pressures. There is also considerable evidence that intense catecholamine stimulation of the heart may have deleterious effects on cardiac structure and function over time. High catecholamine levels, produced either experimentally by intravenous infusion or pathologically by a pheochromocytoma, can damage the myocardium.[10] They can adversely affect the balance between myocardial oxygen supply and demand in patients in whom this ratio is tenuously balanced. While this clearly applies to patients with coronary artery disease, recent studies in an experimental model of heart failure[11] suggest that it may also occur in patients with normal coronary arteries. In either case, myocardial ischemia may further impair myocardial function. Catecholamines may also contribute to the high rate of sudden death by promoting arrhythmias. It is not surprising, therefore, that elevated plasma norepinephrine levels are a risk factor for mortality in patients with CHF.[3,12]

It has recently been shown that high levels of circulating catecholamines are associated with "down regulation"—homologous desensitization—of β-adrenergic receptors. Although the precise mechanisms leading to β-adrenoceptor down regulation are uncertain, there is recent evidence that abnormalities in norepinephrine uptake mechanisms may be involved.[13] In any case, such down regulation leads to decreased myocardial sensitivity to catecholamines over time.[14] This factor may, at least in part, explain the decrease in contractile function and the lack of myocardial functional reserve observed in patients with chronic CHF.

Various renal mechanisms that result in sodium and water retention are activated in CHF. As with venoconstriction, these compensatory changes increase preload and can enhance cardiac output. The plateau portion of the LV function relationship indicates the limit to which increasing the preload can augment the cardiac output. At the same time, the increased volumes move the patient toward the steep ascending portion of the diastolic pressure-volume relationship. Unfortunately, patients with CHF typically retain more salt and water than is necessary for optimal cardiac performance. Excessive salt and water retention fails to increase the cardiac output after a point and is one of the driving forces toward the development of congestive symptoms.

A reduction in cardiac output would be expected to lower the blood pressure if all other variables remained constant. In these patients, however, arterial resistance vessels often become constricted as a compensatory measure to help maintain perfusion pressure. The peripheral arterial tone is regulated systemically and locally by neurohormonal agents, by metabolic products, and by structural changes in the vessels themselves. These factors are summarized in Table 2. Unfortunately, in addition to maintaining the blood pressure, arterial vasoconstriction will increase the afterload, and this tends to have adverse effects on the LV performance as shown in Figure 2.

Therapy for Congestive Heart Failure

Despite the generally poor prognosis for patients with CHF, therapeutic agents can alleviate symptoms and improve the quality of life in the vast majority. The therapeutic approach to CHF must take into account problems caused by the underlying LV dysfunction and those that are brought about by activation of the various compensatory changes throughout the body. In general, drugs used to treat CHF will alter the cardiac performance based on their ability to affect changes in preload, afterload, and contractility. This is not to say, however, that improvements in cardiac performance will necessarily translate into clinical benefits. The dissociation between the hemodynamic effects of a drug and its effects on the important clinical variables is amply documented in the literature. Consequently, in this review we will emphasize therapy for which clinical efficacy has been demonstrated in well-designed trials.

Before initiating a therapeutic regimen or modifying an existent one, it is important to identify any precipitating or exacerbating causes of worsening CHF. Ghali and coworkers reported the relative frequency of various factors precipitating CHF that required admission to a hospital.[15] Although that study was based on observations made in an urban African-American population and might not quanti-

TABLE 2.—*Regulation of Peripheral Vascular Tone*

- Factors associated with vasoconstriction
  - Neurohormonal
    - Catecholamines
    - Angiotensin II
    - Arginine vasopressin
    - Neuropeptide Y
    - Endothelin (and other endothelium-derived contraction factors)
  - Structural changes in arterioles
  - Increased tissue pressure
    - Perivascular edema
  - Other?
- Factors associated with vasodilation
  - Neurohormonal
    - Atrial natriuretic factor
    - Prostaglandins
    - Endothelium-derived relaxation factors
  - Local tissue metabolic products
  - Other?

tatively predict the relative contribution of these factors in other groups of patients, it does provide important insights into the high proportion of potentially preventable causes. Noncompliance with either medications and diet or both accounted for 64% of admissions. Uncontrolled hypertension contributed to 44% of the cases, and cardiac arrhythmias (mostly atrial fibrillation or flutter) were associated with worsening failure in 29%. In the latter instance, however, it is difficult to know if the arrhythmia was the cause or an effect of worsening CHF. Other conditions that should be considered include myocardial ischemia, pulmonary infection or embolism, anemia, environmental factors such as exposure to extremes of temperature, and emotional stress. Additional factors such as the use of medications with negative inotropic effects—β-blockers, calcium channel blockers, and most antiarrhythmic agents—may precipitate clinical deterioration. Nonsteroidal anti-inflammatory agents potentially worsen CHF by causing renal sodium retention, decreasing renal function, and possibly by interfering with prostaglandin-mediated vasodilation.[16] Other less common factors that may lead to a deterioration in patients with CHF are thyrotoxicosis, Paget's disease, and pregnancy.

An important and frequently overlooked aspect of therapy is the dietary restriction of sodium. It is generally recommended that patients be placed on a "no added salt" diet and that they avoid high-sodium-containing foods. This will reduce their daily sodium intake to about 1.5 to 3 grams of sodium—about half the average American intake. More severe CHF (New York Heart Association [NYHA] class IV) may respond to diets restricted to 0.5 to 1.0 grams of sodium per day. Consultation with a dietician is often helpful to the patient and family in identifying particular foods that should be avoided. Dieticians may also provide practical suggestions regarding the use of salt substitutes and spices to maintain an interesting and palatable diet. Physician involvement in this process helps emphasize the importance of the diet, increasing the likelihood of compliance.

The use of salt substitutes merits special consideration. Physicians often fail to take a history of salt substitute use, and patients may or may not consider the importance of the potassium content of these products. This source of potassium can be particularly important in patients using potassium-sparing diuretics and also in patients taking angiotensin-converting enzyme (ACE) inhibitors because these agents tend to increase serum potassium levels. Hyperkalemia resulting from the combination of an increased intake and reduced renal excretion could contribute significantly to morbidity and mortality from ventricular arrhythmias.

Diuretics

Diuretics are an important and usually necessary first step in the pharmacologic treatment of CHF. By promoting renal salt and water excretion, diuretics reduce left ventricular filling pressures. When filling pressures are high and the patient is at the plateau phase of the LV function curve, a reduction in the LV end-diastolic pressure—and pulmonary capillary wedge pressure—can be accomplished without compromising cardiac output. The diuretic dosage can be safely increased until signs and symptoms of pulmonary and systemic congestion are controlled or there is evidence that the forward cardiac output is being compromised. Hypotension, increased blood urea nitrogen (BUN) levels, or symptoms of fatigue and decreased exercise tolerance suggest that the diuretic dosage has increased to the point of reducing the cardiac output.

Although diuretics generally do not increase the cardiac output, there are a few exceptions to this rule. When LV dilation leads to mitral regurgitation due to dysfunction of the subvalvular apparatus, a reduction in ventricular volumes may improve valvular competence and thereby increase the cardiac output. In patients with pulmonary congestion, the relief of dyspnea following effective diuresis has been associated with a reduction in peripheral vasoconstriction presumably on the basis of a decreased sympathetic tone.[17] This would tend to reduce the afterload with a resultant increase in cardiac output. Finally, ventricular wall stress (afterload) is proportional to the left ventricular radius so that a reduction in LV systolic volume would also decrease the afterload directly.

A major problem with diuretic therapy is the associated electrolyte abnormalities. Hypokalemia and hypomagnesemia can be caused by diuretic use, and either disorder predisposes a patient to the development of ventricular arrhythmias. When hypomagnesemia coexists with hypokalemia, potassium replacement alone may not succeed in returning serum potassium levels to a normal range.[18] Repletion of the magnesium deficit can greatly reduce the daily potassium requirements in these patients.[19] Unfortunately, clinically useful estimates of intracellular magnesium concentrations are not widely available, and serum levels may be normal despite the presence of total body magnesium depletion. It is appropriate to replace magnesium if serum levels are low. It is also reasonable to give a trial of magnesium supplement if refractory hypokalemia occurs despite a normal serum level of magnesium. Intravenous or intramuscular replacement with magnesium is well tolerated, although it may require several grams to replace the intracellular deficit. Although oral magnesium salts have been variably absorbed and have caused diarrhea in the past,[19] some of the newer preparations appear to be effective and are better tolerated.

Table 3 summarizes characteristics of the commonly used diuretic agents. These agents are distinguished from each other by their site of action, potency, and side effects. Combination diuretic therapy has become increasingly popular over the past few years based on its efficacy in solving two common problems. A patient who is relatively refractory to high doses of a loop diuretic like furosemide often responds dramatically to the addition of metolazone. The reason for this is that the two agents act on different sites within the nephrons. Similarly, adding a potassium-sparing diuretic is useful in treating severe or refractory hypokalemia induced by the loop diuretics. Because ACE inhibitors tend to raise potassium levels, the combination of a potassium-sparing diuretic and an ACE inhibitor should be avoided. Likewise, potassium-sparing diuretics should not be given to diabetic patients with evidence of renal tubular acidosis, as their aldosterone deficiency renders them susceptible to the development of life-threatening hyperkalemia.[20]

Digitalis

Digitalis is the drug of choice in patients with CHF who are in atrial fibrillation. Despite two centruries of experience with digitalis preparations, their use in patients with CHF and sinus rhythm has been widely debated during the past ten years. A great deal of uncertainty regarding the efficacy of digitalis can be ascribed to the fact that most studies examining this question before 1984 were inadequate in terms of blinding or controls.[21] Many of these studies also included patients who were not likely to respond to

therapy owing to a lack of symptoms, the presence of valvular disease, or diastolic abnormalities as the primary cause of CHF. More recently, there is evidence from a few well-designed trials that adding digitalis preparations to the medical regimen of patients with CHF due to LV dysfunction will substantially improve their cardiac function and clinical state.[22-28] Patients who have an S_3 gallop, LV enlargement, or NYHA class III to IV symptoms before treatment are most likely to have clinical improvement with digitalis therapy.[21]

Several recent reports also suggest that digitalis therapy may be of value in treating milder degrees of failure. In a comparison of milrinone and digoxin, 230 patients with moderate CHF (NYHA class II and III) were randomly selected to receive a diuretic with one of the following supplements: placebo, digoxin, milrinone, or a combination of digoxin and milrinone.[28] In this double-blind trial, only 15% of patients treated with digoxin had evidence of clinical deterioration compared with 47% of the placebo group. Digoxin was associated with substantially increased exercise tolerance, and there was no obvious increment in benefit by adding milrinone.

Another multicenter, double-blind, placebo-controlled study compared captopril treatment and digoxin treatment during maintenance therapy with diuretics in 300 patients with mild CHF—87% had NYHA class II CHF.[25] The results of this study showed that patients treated with either digoxin or captopril had 50% fewer emergency department visits and fewer hospital admissions than the placebo group. It is worth noting that although no study has documented an improvement in survival attributable to the use of digitalis,[29] both of the clinical trials showing a reduction in mortality by vasodilators have included digitalis as part of the treatment regimen.[30]

One reason for the reluctance to use digitalis preparations in the treatment of CHF has been the issue of safety. Although the prevalence of toxicity in patients who are receiving digitalis while in hospital has been estimated to be in the range of 5% to 15%,[31] the safety profile of digitalis in recent controlled clinical trials has been good. In none of these trials has the incidence of adverse reactions due to digitalis exceeded the rate associated with placebo or control treatment.[29] Nonetheless, the possibility of digitalis toxicity requires a consideration of risk factors and drug interactions that would enhance the likelihood of its occurrence. Factors associated with toxicity include advanced age, renal insufficiency, anorexia, and pulmonary disease. Hypokalemia and hypomagnesemia exacerbate digitalis toxicity, and, as mentioned, both may be induced by diuretic use.[32]

Digoxin interacts with a number of agents commonly used in patients with congestive heart failure. The interactions most likely to lead to digitalis toxicity involve quinidine,[33] amiodarone,[34,35] and verapamil.[36] As a general rule, the serum digoxin concentration will reach a new steady state within five elimination half-lives. After quinidine or verapamil therapy is initiated, it is prudent to decrease the digoxin dose by half and check a digoxin level in about a week, assuming the patient has normal renal function.[37] The time course of the interaction with amiodarone is more difficult to predict, but the dosage should be similarly reduced.

Vasodilating Agents

As already mentioned, the development of vasoconstriction in patients with CHF can have adverse effects on cardiac performance. By relaxing smooth muscle tone in peripheral resistance vessels, arterial dilators can reduce the LV afterload. This results in an upward shift of the LV function curve so that at any given level of preload, the cardiac output will be increased. Venodilators relax venous capacitance vessels, thereby increasing the amount of blood that is pooled in the periphery. The reduction in the amount of venous return to the heart reduces ventricular volumes and filling pressures. The effect of the venodilators on the LV function curve is similar to that of the diuretic agents. As with the diuretics, venodilators have little effect on forward cardiac output when the patient is at the plateau portion of the LV function curve. They can, however, significantly reduce cardiac output when the patient is at the ascending limb of the LV function curve. Many agents produce both arterial and venous vasodilatory effects. The characteristics of vasodilators that are currently used in the treatment of chronic CHF are summarized in Table 4.

In practice, there has been a disparity between the acute hemodynamic and long-term clinical effects of the vasodilating drugs. Consequently, not all vasodilators are effective in treating CHF. Neither minoxidil,[38] a potent arterial dila-

TABLE 3.—*Characteristics of Commonly Used Diuretic Drugs*

Drug	*Usual Dosage Schedule, mg/d*	*Onset of Effect*	*Peak Effect*	*Duration*	*Drug-Specific Side Effects*	*Side Effects by Class*
Thiazide and related diuretics						
Chlorothiazide	500-1,000	1 h	4 h	6-12 h	...	Hypokalemia, hypercalcemia, hypochloremic alkalosis, hyperglycemia, hyperuricemia, hypertriglyceridemia
Hydrochlorothiazide	50-100	2 h	4 h	>12 h	...	
Chlorthalidone	50-100	2 h	6 h	24-72 h	...	
Metolazone	5-20	1 h	2-4 h	12-24 h	...	
Loop diuretics						
Furosemide	40-600	PO 1 h IV 5 min	1-2 h 30 min	6 h 2 h	Sulfa-allergy, rashes, hyperglycemia	Hypokalemia, hypochloremic alkalosis, hyperuricemia, ototoxicity
Ethacrynic acid	50-400	PO 30 min IV 15 min	2 h 45 min	6-8 h 3 h	Increased warfarin effect, diarrhea	
Bumetanide	1-4	PO 1 h IV 5 min	1-2 h 30 min	6 h 2 h	Nausea, rashes, myalgias, hyperglycemia	
Potassium-sparing diuretics						
Amiloride	5-10	1 h			Glucose intolerance	Hyperkalemia, hyperuricemia
Spironolactone	25 QID	Gradual	1-2 d	2-3 d	Gynecomastia, impotence	
Triamterene	100-300	1 h	2-3 h	7-9 h	Renal stones	

IV = intravenously, PO = [per os] orally, QID = 4 times a day

tor agent, nor prazosin,[39] a mixed arterial and venodilator, has proved to be of value in the long-term management of chronic CHF. Hydralazine hydrochloride, a direct-acting, predominantly arterial-dilating agent, was one of the first vasodilator drugs to be used in the treatment of CHF. Despite initial enthusiasm, evidence from clinical trials has failed to show improved exercise tolerance or relief of symptoms with long-term hydralazine therapy.[40] In patients with aortic or mitral regurgitation, however, the drug appears to be useful. We have previously shown that in this setting, hydralazine can redistribute the total LV stroke volume such that the forward stroke volume is increased and the regurgitant stroke volume is reduced.[41,42] These changes have been associated with clinical improvement in at least some patients with aortic or mitral insufficiency and CHF.[43,44] There is also evidence that, when administered early in the course of aortic regurgitation, hydralazine therapy is associated with a reduction in LV volumes over time.[45] Because the extent of volume overload is a strong predictor of future deterioration,[46] these findings suggest that long-term hydralazine therapy may delay the progression to valve replacement in these patients.

The long-acting nitrate preparations have been reported to improve exercise tolerance and relieve symptoms in patients with CHF. Considering their antianginal effects, nitrates are particularly useful when CHF complicates coronary artery disease. As with the use of prazosin, tachyphylaxis to the vasoactive effects of nitrates can develop rapidly and can limit their efficacy in treating CHF.[47,48] Nitrate tolerance has been extensively reviewed recently.[48] The mechanisms leading to nitrate tolerance may relate to continuous binding to the poorly characterized nitrate receptor or oxidation of the receptor by prolonged therapy. Tachyphylaxis can be minimized by drug-free intervals (between 6 and 12 hours appears to be sufficient), slightly longer dosage intervals (for example, isosorbide dinitrate given every 8 instead of every 6 hours), and possibly by administering sulfhydryl donors like *N*-acetylcysteine.[49] Of interest is the fact that the ACE inhibitor captopril contains a sulfhydryl group, and it, too, may be useful in counteracting nitrate tolerance.[50,51]

The Veterans Administration Vasodilator Heart Failure Trial was the first large clinical trial showing that treatment can improve survival rates in patients with CHF.[52,53] In this study, a group of 642 men with moderate to severe chronic CHF who remained symptomatic despite therapy with digitalis and diuretics were randomly selected to receive placebo, prazosin, or the combination of isosorbide dinitrate and hydralazine. Cumulative mortality was substantially reduced in the hydralazine-isosorbide group compared with that in either the prazosin or placebo groups. Enthusiasm for this particular combination, however, has been limited by the fact that symptomatic improvement and an increased exercise time were not demonstrated. Furthermore, only 55% of patients in the hydralazine-isosorbide group tolerated the full dosage of both drugs, with around 32% discontinuing one or both agents.

Angiotensin-converting enzyme inhibitors have been an extremely important addition to our therapeutic choices. The central role of the renin-angiotensin system in the compensatory response to CHF gives ACE inhibitors unique advantages over other vasodilators. There is convincing evidence that ACE inhibitors lessen symptoms and improve exercise capacity[54,55] in patients with severe CHF. The Cooperative North Scandinavian Enalapril Survival Study compared the effects of enalapril with placebo on survival rates in patients with class IV CHF despite standard therapy consisting of digitalis, diuretics, and, in some cases, non-ACE inhibitor vasodilators.[7] The study was terminated prematurely because of the consistent benefit associated with enalapril treatment. The 12-month mortality was 52% in the placebo group and only 36% in the enalapril group. Patients treated with enalapril were also much more likely to have improvement in functional class and were less likely to require additional cardiovascular medications. In contradistinction to the Veterans Administration Vasodilator Heart Failure Trial, similar percentages of patients receiving placebo or enalapril were withdrawn, suggesting that ACE inhibitors are a far more useful option than the combination of hydralazine and isosorbide dinitrate.

There is also evidence that ACE inhibitors can reduce the occurrence of clinical deterioration, improve functional class, and increase exercise capacity in patients with milder degrees of failure.[25,56] A recent randomized, double-blind, placebo-controlled trial showed that captopril provided substantial benefits over diuretic therapy alone in terms of exercise time, need for admission to hospital or emergency department treatment, and functional class in a group of patients with mild to moderate CHF.[25]

The prophylactic administration of ACE inhibitors to survivors of myocardial infarctions with evidence of LV dysfunction may prove to be a valuable means of protecting against future deterioration. Pfeffer and associates have reported that captopril therapy after experimental myocardial infarction in rats prevented an elevation of the LV end-diastolic pressure, improved the ejection fraction, reduced LV volumes, and normalized LV wall stiffness.[57] Most important, there was a significant reduction in mortality in rats with moderate to large infarctions. Two randomized, double-blind trials in patients have reported that the early

TABLE 4.—*Characteristics of Commonly Used Vasodilator Drugs*

Agent	*Dosage, mg*	*Duration*	*Drug-Specific Side Effects*	*Side Effects by Class*
ACE inhibitors				
Captopril	6.25-50 q 8 h	4-8 h	Neutropenia, loss of taste	Hypotension, hyperkalemia, renal dysfunction, proteinuria, cough, dizziness, angioedema
Enalapril maleate	2.5-10 q 12 h	12-24 h	Abnormal liver function	
Lisinopril	10-40 q 24 h	>24 h	Diarrhea	
Arterial dilators				
Hydralazine HCl	50-100 q 8 h	6-12 h	GI upset, lupuslike reaction	Postural hypotension, flushing, headache
Venodilators				
Nitroglycerin				Headache, dizziness, flushing
Oral	6.5-20 q 6 h	4-6 h		
Ointment	1-6 in q 6 h	4-6 h		
Transdermal	5-20 q 24 h	24 h		

ACE = angiotensin-converting enzyme, GI = gastrointestinal, HCl = hydrochloride, q = [quaque] every

administration of ongoing ACE inhibitor therapy after a myocardial infarction may delay progressive LV dilatation, particularly in patients with extensive amounts of damage.[58,59]

Side effects that limit the use of ACE inhibitors in patients with mild to moderate degrees of CHF are uncommon.[25] They may occur somewhat more frequently in patients with severe CHF. Although most patients have an initial reduction in blood pressure, hypotensive symptoms are uncommon and the blood pressure usually returns toward the pretreatment range over time. Patients at risk for symptomatic hypotension and renal insufficiency developing will have the following risk factors: hyponatremia,[60] intensive diuretic therapy, functional class IV status, concurrent therapy with other vasodilators, or borderline hypotension before initiation of the drug regimen. Therapy should not be withheld from such patients, however, as they are the most likely to benefit from vasodilator therapy. Several measures may help avoid complications to new or increased doses of ACE inhibitors:

- Reduce the dose of diuretics or hold a dose immediately before initiating treatment with ACE inhibitors,
- Initiate therapy using low doses of a shorter-acting agent such as captopril,
- Gradually increase the dose as tolerated,
- Instruct outpatients to start new or increased doses immediately before retiring at night.

In patients at particularly high risk for complications, new doses should be administered in a setting where the patient can be observed and therapy to support the blood pressure can be instituted if necessary. Increases in laboratory indicators of renal function such as the BUN and creatinine levels are not uncommon when therapy with ACE inhibitors is initiated. They are usually transient and reversible, but some degree of worsening may persist. It has been our practice to continue ACE inhibitor therapy despite modest increases in the BUN or creatinine levels in patients who show evidence of clinical improvement. In addition to hypotension and renal insufficiency, other problems associated with the use of ACE inhibitors include cough, rash, taste disturbances, and hyperkalemia.

Positive Inotropic Agents and β-Blockers

Although positive inotropic agents have an established role in the initial management of patients admitted to hospital with severe acute CHF, clinical trials have thus far failed to provide convincing evidence that long-term therapy with any of the investigational inotropic agents will provide benefits above and beyond those of the currently available drugs.[28] Approval of these agents has been hampered by a relatively high incidence of side effects to some of the agents and the development of tachyphylaxis to others. In addition, pooled data raise the possibility that mortality in severe CHF may be higher with these agents than that reported in historical controls treated with vasodilators.[61] Ongoing studies with a variety of inotropic agents should provide more definitive information regarding their value in treating patients who have chronic CHF.

An alternative approach to the treatment of CHF is the use of β-blockers. Despite the fact that these agents were once thought to be contraindicated when LV dysfunction was present, there is now some evidence supporting their use as therapy. Theoretically, β-blockers might be able to prevent some of the adverse consequences of excess catecholamines described previously (ventricular arrhythmias, ischemia, myocardial damage, and down regulation of β-adrenergic receptors). Clinical trials in a limited number of patients suggest that β-blockers may improve exercise tolerance, relieve symptoms, and increase the ejection fraction over time.[62-64] Because these results are based on only a small number of patients, they need to be confirmed in larger clinical trials. Until results from such trials are available, the use of β-blockers must be considered experimental.

Treatment of Diastolic Dysfunction

The treatment of CHF due to LV diastolic abnormalities is challenging and different from the approach to LV systolic dysfunction. To rationally treat this disorder, it is first necessary to correctly diagnose its presence. The identification of left ventricular diastolic dysfunction can be difficult because the clinical signs and symptoms are often similar to those arising from systolic dysfunction. Diastolic dysfunction should be suspected when CHF develops in patients with a normal-sized left ventricle, in patients with hypertension (particularly when there is evidence of LV hypertrophy), in patients whose condition deteriorates with the usual therapy for CHF, in patients with evidence of aortic outflow obstruction, in patients with diabetes mellitus, and in the elderly.[65,66] The demonstration of normal or only mildly impaired systolic function and the absence of other lesions—such as valvular or pericardial disease or intermittent myocardial ischemia that can result in transient increases in LV stiffness—in a patient with signs and symptoms of CHF should raise a suspicion that diastolic dysfunction is present. Definitive criteria for diagnosing diastolic dysfunction using noninvasive testing are still evolving.

Because the basic abnormality is one of diastolic filling of the left ventricle, positive inotropic or afterload-reducing agents are usually ineffective. Diastolic dysfunction is best treated by cautious diuresis.[67] As depicted in Figure 1, however, the LV pressure-volume relationship has a steep slope so that these patients tend to be extremely sensitive to changes in volume status. An overdiuresis in these patients can lead to profound reductions in cardiac output. Conversely, fluid retention rapidly produces edema and pulmonary congestion.

In patients with diastolic dysfunction due to hypertrophic cardiomyopathy, calcium channel blockers may both lessen symptoms and improve diastolic compliance.[68-70] These drugs may not be effective when hypertrophy develops on the basis of other causes such as aortic stenosis.[71] When myocardial ischemia or hypertension is the cause of diastolic dysfunction, treatment of the underlying disease may be helpful in preventing the signs and symptoms of heart failure. In planning the treatment of hypertension, the use of drugs that are associated with the regression of LV hypertrophy (such as the β-blockers, calcium antagonists, or ACE inhibitors) is preferred.

Treatment of Systolic Dysfunction

Precipitating factors should be identified and corrected as part of the initial approach or when adjusting therapy in response to worsening CHF. Salt restriction is an important nonpharmacologic means of reducing congestive symptoms and should be considered in all patients. Most patients, however, will require the addition of diuretic therapy. It is usually appropriate to initiate therapy with a potent loop diuretic. The need to assess for and correct electrolyte abnormalities in patients with CHF who are receiving diuretics cannot be overstressed.

In addition to diuretics, both an ACE inhibitor and digitalis therapy should be given to patients with advanced CHF. The ACE inhibitors have been convincingly shown to increase exercise tolerance, relieve symptoms, and, in patients with class IV CHF, improve the survival rate. Digitalis therapy is recommended on the basis of recent studies verifying its efficacy even in patients with sinus rhythm and only moderate degrees of CHF. In addition, the beneficial effects of vasodilators in the survival of patients with advanced heart failure generally have been shown in patients concurrently receiving digitalis.

Patients with a milder degree of CHF are likely to do better when either digoxin or an ACE inhibitor is added to diuretic therapy. Currently available information suggests that this approach will decrease the likelihood of clinical deterioration, and it may improve exercise capacity. Although pharmacologic therapy for asymptomatic LV dysfunction has not yet been conclusively shown to be of value, early treatment with ACE inhibitors may be helpful in preventing progressive LV dilatation after a large myocardial infarction.

Future Trends

Over the past 25 years there have been many advances in both our understanding of the pathophysiology of CHF and in our ability to care for patients with this syndrome. In particular, information revealing the central role of vasoconstriction in the pathogenesis of CHF and the neurohormonal mechanisms involved has allowed more specific and potent therapies to be devised.

Many important questions need to be answered as we attempt to further refine the treatment of CHF. Whether or not treatment with ACE inhibitors will improve survival in patients with mild to moderate CHF and whether or not these agents will be of value in patients with asymptomatic LV dysfunction are issues currently being addressed in clinical studies. Both β-blockers and positive inotropic agents are currently being evaluated in large-scale randomized trials, and information regarding their efficacy in treating CHF should be available in the near future.

Because sudden death accounts for 35% to 45% of all mortality in patients with CHF,[72] further research in this area remains of paramount importance. A better description of the rhythm and conduction abnormalities involved is clearly needed.[73] The value of antiarrhythmic therapy and electronic defibrillator-pacemaker devices in preventing sudden death also needs to be defined.

Further insights into the pathogenesis of the progressive deterioration in myocardial structure and function that take place after an initial insult are needed. This information is likely to come from studies assessing myocardial function on a cellular and molecular level. It is hoped that the pathways that are illuminated by such studies will result in the formulation of drug therapies that can halt the downward spiral of events.

Ultimately, CHF needs to be prevented more effectively through improved intervention on the underlying diseases leading to systolic or diastolic abnormalities of the left ventricle. Until then, we must strive to support the dysfunctional myocardium and manipulate the complex compensatory mechanisms unleashed by myocardial dysfunction in ways that minimize symptoms, prevent further damage to the heart, and prolong life.

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Essential Hypertension—Where Are We Going?

Discussant
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This discussion was selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from a transcription, it has been edited by Homer A. Boushey, MD, Professor of Medicine, and Nathan M. Bass, MD, PhD, Associate Professor of Medicine, under the direction of Lloyd H. Smith, Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine.

(Ives HE: Essential hypertension—Where are we going? West J Med 1990 Oct; 153:415-420)

FLOYD C. RECTOR, MD*: *Great advances have been made in the treatment of hypertension, and long-term therapy has proved effective in reducing the risk of cardiovascular disease. The costs and complications of current therapy are often troublesome, and the development of more effective treatment ultimately requires defining the mechanisms underlying the disease. For common, "essential" hypertension, these mechanisms are unknown, but several attractive and instructive theories have been proposed. Harlan Ives, MD, Chief of the Division of Nephrology, has been active in studies of these theories and reviews their promise and problems in efforts to better understand and more effectively treat the disease.*

HARLAN E. IVES, MD, PhD†: Despite intensive research over many years, the pathogenesis of essential hypertension remains mysterious. Patients with essential hypertension do not have the high circulating levels of renin that characterize renal artery stenosis, nor do they have the volume overload and suppressed renin-angiotensin system that characterizes primary hyperaldosteronism. At an intravascular volume that is close to normal, patients with essential hypertension maintain an elevated vasomotor tone, or an elevated vasomotor tone develops with increased salt intake. A mechanism is needed to explain this increased vasomotor tone.

One of the major hypotheses for the pathogenesis of essential hypertension focuses on the ion transport systems that regulate salt excretion by the kidney and that also control the intracellular ionic milieu of all cells. It is proposed that factors that regulate salt transport by renal epithelial cells may also affect the intracellular ionic milieu in vascular smooth muscle cells. By altering the intracellular sodium (Na^+), calcium (Ca^{2+}), hydrogen (H^+), or other ions, these transport systems have the potential to regulate vascular smooth muscle contractile activity. Defects in the activity or regulation of one or more of these transport systems have been proposed to cause certain forms of hypertension. In this review I will critically assess the basis for this contention and propose several areas for future investigation into the pathogenesis of essential hypertension.

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Ion Transport Defects and Hypertension

Most of the recent thinking on the role of ion transport defects in hypertension flows from the hypothesis, first broached by Haddy and Overbeck[1] and by Blaustein,[2] that essential hypertension is caused by the production of circulating Na^+ transport inhibitors acting on renal epithelial cells and vascular smooth muscle cells. This hypothesis drew much of its force from earlier observations by Dahl and co-workers that salt-sensitive hypertension in rats could be transferred by renal transplantation or by the exchange of fluids in parabiotic experiments.[3] This led to the idea that, in response to salt loading, the kidney produces a circulating substance that causes both natriuresis and vasoconstriction. Work carried out over a number of years by Overbeck, Pamnani, Clough, and Haddy (reviewed by Haddy and Overbeck[1]) suggested that this circulating substance might be an inhibitor of the Na^+-potassium ion (K^+) adenosine triphosphatase (ATPase), or Na^+, pump. Such an inhibitor would cause natriuresis by reducing Na^+ reabsorption by renal epithelial cells.

Sodium pump inhibitors would also be expected to affect vascular smooth muscle function. In these cells, the inhibitors would cause the cell Na^+ content and volume to rise and the membrane potential to fall. Blaustein argued that increased intracellular Na^+, acting on a plasma membrane Na^+-Ca^{2+} exchange system, would then lead to increased intracellular Ca^{2+} (Figure 1).[2] Increased vascular smooth muscle cell Ca^{2+}, by its well-known action on the contractile machinery, would in turn lead to the contraction of vascular smooth muscle cells or increased responsiveness to vasoconstrictors. Increased vascular tone would raise the blood pressure, contributing to the desired natriuresis. In normotensive persons, a steady state would be achieved wherein Na^+ intake would be matched by Na^+ excretion at a plasma volume and blood pressure close to normal. A "salt-sensitive" hypertensive person, by failing to excrete the Na^+ load at an adequate rate, would remain volume overloaded, would continuously produce the natriuretic or hypertensive substance, and would become chronically hypertensive as long as salt intake remained unchanged.

This hypothesis, while seductive in its simplicity and broad explanatory power, has never been adequately sub-

This work is supported in part by grants (DK-34127 and HL-41210) from the National Institutes of Health and from the National Dairy Board (administered in cooperation with the National Dairy Council). Dr Ives is an Established Investigator of the American Heart Association.

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ABBREVIATIONS USED IN TEXT

ATPase = adenosine triphosphatase
UCSF = University of California, San Francisco

stantiated. Numerous studies by various investigators have examined the Na^+-K^+ ATPase activity, as well as a number of putative circulating inhibitors (digitalis-"like" factors) in normotensive and hypertensive persons. Space prohibits a thorough review of this information, which has been extensively reviewed elsewhere. Studies of both human and experimental hypertension, however, have failed to show a consistent correlation between Na^+-K^+ ATPase activity and blood pressure. While circulating inhibitors of the Na^+ pump have been found,[4] their precise chemical makeup is not clear, the stimulus to their production is unknown, and, most important, it is not known whether they actually cause hypertension. In a recent provocative editorial, Kelly and Smith even question the assumption that the digitalis binding site on the Na^+-K^+ ATPase is the receptor for a circulating factor.[5] They raise the possibility that this site may play a role in intracellular trafficking of the enzyme. The only convincing natriuretic substance found thus far, atrial natriuretic factor, is not a potent inhibitor of Na^+-K^+ ATPase, and, contrary to the hypothesis outlined above, it is not a vasoconstrictor but a vasodilator.

Variants of the Haddy-Blaustein hypothesis argue that abnormal cell Na^+ in vascular smooth muscle cells might not arise from decreased Na^+ efflux through Na^+-K^+ ATPase but, rather, from increased Na^+ uptake through Na^+-entry pathways. A similar defect on the apical membrane of renal epithelial cells would enhance renal sodium reabsorption and thus reduce urinary Na^+ excretion. Such increased Na^+ entry into renal epithelial cells would not be expected as a response to volume overload but, rather, may play a role in the development of volume overload. Sodium entry pathways that could participate in enhanced Na^+ uptake include the Na^+-H^+ exchanger, the Na^+, K^+, chloride (Cl^-) transporter, and the Na^+ channel. Of these, the system that has received the most recent attention is the Na^+-H^+ exchanger.

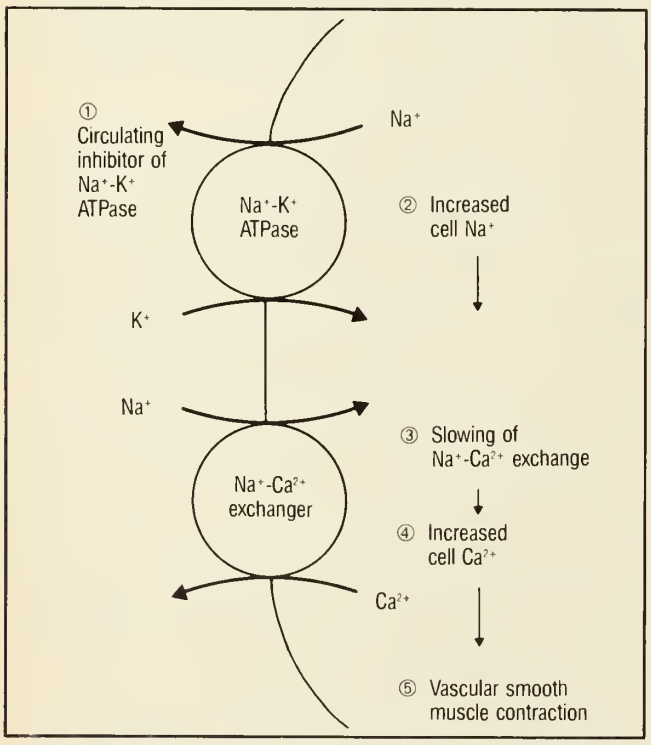

Figure 1.—The Blaustein hypothesis proposes that circulating sodium ion (Na^+) transport inhibitors elaborated during volume overload might lead to a contraction of vascular smooth muscle cells by an elevation in the intracellular calcium ion (Ca^{2+}) concentration. ATPase = adenosine triphosphatase

Sodium-Lithium and Sodium-Hydrogen Exchange

The possibility that Na^+-H^+ exchange might be involved in the development of hypertension was first brought forward after the discovery ten years ago that erythrocytes from hypertensive patients have increased erythrocyte Na^+-lithium (Li^+) exchange activity when compared with normotensive persons.[6] While it is still not clear what role the Na^+-Li^+ countertransport plays in cellular physiology, it seems plausible that this system represents a mode of operation of the ubiquitous Na^+-H^+ exchanger. Among its many functions, the Na^+-H^+ exchanger is the most important Na^+ uptake pathway on the apical membrane of the proximal tubule epithelial cell and therefore plays an essential role in Na^+ transport by this nephron segment (Figure 2). It is still not known whether red cell Na^+-Li^+ exchange and proximal tubule Na^+-H^+ exchange represent the same transport system, but it is known that Li^+ is an excellent substrate for the Na^+-H^+ exchanger[7] and that protons interact with the erythrocyte Na^+-Li^+ exchanger.[8] On the other hand, Na^+-H^+ exchange is amiloride sensitive,[7] but erythrocyte Na^+-Li^+ exchange is resistant to this agent.[9] Taken together, the data seem to suggest that the renal Na^+-H^+ exchanger and the red cell Na^+-Li^+ countertransport system are not identical but may represent different modes of operation of the same or related transport systems.

The idea that Na^+-H^+ exchange is involved in the pathogenesis of hypertension has been bolstered by several recent observations. First, cultured vascular smooth muscle cells from spontaneously hypertensive rats had significantly higher Na^+-H^+ exchange activity than cells from normotensive Wistar-Kyoto rats.[10] In other work, intact blood vessels from 5-week-old spontaneously hypertensive rats were more alkaline than similar vessels from Wistar-Kyoto rats, possibly due to increased Na^+-H^+ exchange in the former. A study in humans also supports the idea that hypertension is related to increased activity of Na^+-H^+ exchange. Platelets from untreated hypertensive subjects exhibited enhanced swelling on adding sodium propionate when compared with normal controls.[11] This activity is probably due to increased

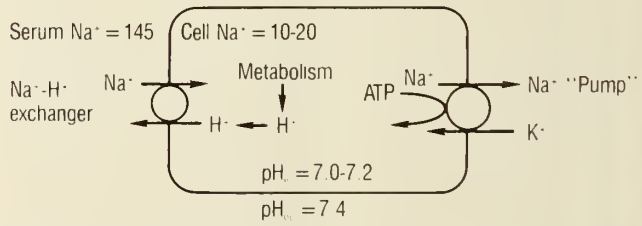

Figure 2.—The sodium-hydrogen ion (Na^+-H^+) exchanger is found in virtually all cells and is responsible for removing acid generated by metabolic processes within the cell. The Na^+-H^+ exchanger uses as its energy source the Na^+ gradient generated by the Na^+ pump. In renal proximal tubule epithelial cells, the Na^+-H^+ exchanger is localized to the tubular lumen, and the Na^+ pump is on the opposite side of the cell, facing the circulation. This disposition of the transport systems enables the cell to effect net transepithelial Na^+ absorption and H^+ secretion. The fact that common ion transporters are used by renal epithelial cells to effect salt transport raises the possibility that agents which regulate salt transport in the kidney might also affect the intracellular ionic milieu in other cells, including vascular smooth muscle cells. ATP = adenosine triphosphate

Na^+-H^+ exchange in the platelets obtained from hypertensive subjects.

Is increased activity of Na^+-H^+ or Na^+-Li^+ exchange causally related to hypertension, or is it an epiphenomenon arising from other alterations in erythrocytes, platelets, and smooth muscle cells from diseased arteries? Before trying to answer this question, we should briefly consider the mechanisms by which Na^+-H^+ exchange activity can be increased. The regulation of the Na^+-H^+ exchanger in vascular smooth muscle is complex and appears to involve allosteric mechanisms, covalent modification, de novo synthesis, and physical alterations of the membrane. The binding constants for Na^+ and H^+ on the exchanger are close to their physiologic concentrations within the cell. Therefore, changes in the cell pH or cell Na^+ will affect exchanger activity allosterically. Numerous growth factors and vasoconstrictors (including angiotensin II, vasopressin, and endothelin) activate the exchanger through second messenger systems. These have not been fully elucidated, but one such messenger appears to be diacylglycerol, acting on protein kinase C. This enzyme presumably phosphorylates the exchanger or a related membrane protein. Certain hormones (thyroid, glucocorticoids) and environmental factors (acidosis, hypokalemia) appear to increase renal epithelial Na^+-H^+ exchange over hours to days, probably by de novo synthesis of the transporter. This phenomenon may also occur in vascular smooth muscle, but this has not been carefully examined. Finally, osmotic agents through cell shrinkage dramatically activate the exchanger in many cell types, including vascular smooth muscle. The point of this brief summary is that increased Na^+-H^+ exchange activity might be a primary defect in hypertension, or, more likely, it might be a secondary phenomenon arising from altered intracellular Na^+ or pH, increased angiotensin II, vasopressin, endothelin, glucocorticoids, or even shape changes in the cells under study. To date, there is no convincing evidence that increased Na^+-H^+ exchange is a primary defect in hypertension.

Canessa and colleagues and other investigators have found that hypertensive subjects and their normotensive relatives exhibited comparably increased erythrocyte Na^+-Li^+ countertransport, suggesting that increased activity may be a predisposing genetic factor but that it does not itself cause increased blood pressure.[6] Several groups have reported lower rates of red cell Na^+-Li^+ countertransport in African Americans compared with whites; furthermore, they find no relationship between transport and blood pressure in African Americans.[12] With regard to Na^+-H^+ exchange, Livne and associates found that patients with treated hypertension had significantly lower rates of platelet Na^+-H^+ exchange than those with untreated hypertension.[11] These findings suggest that differences in the phenotypic expression or activation of the Na^+-H^+ exchange may be associated with hypertension but actually argue against a causal role for increased transport in the disease.

If increased Na^+-H^+ exchange is indeed a primary defect in essential hypertension, the link between its operation and increased vasomotor tone has yet to be made. Increased Na^+-H^+ exchange activity could have several effects on the vascular smooth muscle cell, including increased cell Na^+, increased pH, and increased cell volume. According to the Blaustein hypothesis, increased cell Na^+ would elevate cell Ca^{2+} by action of the Na^+-Ca^{2+} exchange system.[2] Sodium-calcium exchange has a well-established role in Ca^{2+} metabolism in nerve and cardiac muscle where it was originally described. Although Na^+-Ca^{2+} exchange activity has been found by a number of investigators both in intact vascular smooth muscle cells[13] and in plasma membranes from these cells,[14] its physiologic role in vascular smooth muscle has been surprisingly difficult to ascertain.

Sodium-Calcium Exchange

Isolated plasma membrane vesicles have been the preparation of choice for the study of many membrane transport systems. Unfortunately, Na^+-Ca^{2+} exchange activity in smooth muscle membranes appears to be low, at most 1% of that found in cardiac muscle membranes.[14] This may be due to a loss of activity or activating factors in the preparation. Alternatively, Na^+-Ca^{2+} exchange may not be abundant in smooth muscle.

Early studies with intact vascular smooth muscle systems clearly showed that replacing medium Na^+ with other cations significantly increased isotopic Ca^{2+} influx and caused contraction of vascular strips (reviewed by Blaustein[2]). These findings were interpreted to mean that the plasma membrane of vascular smooth muscle cells contains an Na^+-Ca^{2+} exchange system and that Na^+ removal leads to rapid Na^+ efflux and Ca^{2+} entry. The removal of extracellular Na^+, however, is a drastic maneuver with several potential nonspecific effects. These include alterations in surface charge, membrane potential, Ca^{2+} or other ion channel activity, and Na^+ pump activity. Any of these secondary effects could alter the contractile state or Ca^{2+} transport nonspecifically. The interpretation of such experiments is also clouded by the possibility of Na^+-Ca^{2+} exchange at extracellular Ca^{2+} binding sites. More recently, Smith and co-workers have found that the removal of extracellular Na^+ reveals abundant Na^+-Ca^{2+} exchange activity in cultured aortic smooth muscle cells. Such activity is latent, however, unless the cell Na^+ content is raised from the basal value of 7 mmol per liter to approximately 25 mmol per liter.[13] In the platelet, a cell often used as a model for vascular smooth muscle, neither Na^+ removal nor ouabain alter the intracellular Ca^{2+}.[15] Thus, Na^+-Ca^{2+} exchange has been an elusive link in transport theories of hypertension. Further work in this area is essential before we can accept the idea that this transport system plays a central role in the pathogenesis of hypertension.

Sodium-Hydrogen Exchange and Intracellular Calcium: Is There a Link?

Even if we accept the hypothesis that Na^+-Ca^{2+} exchangers play an important role in vascular smooth muscle Ca^{2+} metabolism, it is not clear that physiologic changes in intracellular Na^+ are sufficient to alter cell Ca^{2+} significantly in vascular smooth muscle. Blaustein argued that the Na^+-Ca^{2+} exchange would carry three Na^+ ions and would therefore be highly sensitive to small changes in Na^+ concentration.[2] To test this hypothesis, Mitsuhashi, working in my laboratory, asked whether physiologic alterations in the Na^+-H^+ exchange activity would alter intracellular Ca^{2+} in cultured vascular smooth muscle cells.[16] She used three potent stimuli of Na^+-H^+ exchange. The first was phorbol myristate acetate, which works by activating protein kinase C and which is also known to cause contraction of vascular smooth muscle. The second was osmotically induced cell shrinkage, and the third was cell acidification by ammonium chloride prepulse. Surprisingly, all three stimuli activated the Na^+-H^+ exchange as expected, but none of them had any measurable effect on the intracellular Ca^{2+}.[16] Other investigators, working with different cell types, have shown that in some cases phorbol esters activate the Na^+-H^+ exchanger but actually decrease the cell Ca^{2+} content.[17] If

such potent stimuli of Na^+-H^+ exchange do not increase the cell Ca^{2+} concentration, it is difficult to envisage how small changes in the Na^+-H^+ exchange such as those reported in platelets[11] could be expected to increase the cell Ca^{2+} content.

Calcium and the Mechanism of Contraction of Vascular Smooth Muscle

Most hypotheses linking abnormalities in ion transport to hypertension consider intracellular Ca^{2+} as the final common mediator of vascular tone. It is surprising that this assumption receives relatively little debate because the control of vascular smooth muscle tone appears to be more complex than this. Assumptions about the primacy of Ca^{2+} regulation in vascular smooth muscle derive from well-established information obtained from skeletal and cardiac muscle. In these systems, the myosin ATPase is regulated by the troponin-tropomyosin system. Calcium binds to troponin C, causing a conformational change that is transmitted to the remainder of the troponin complex and to tropomyosin. These conformational changes allow actin to interact with myosin and to activate the myosin ATPase. Myosin-ATPase activity induces movement of the myosin head along the actin strand. Thus, contractile force and cell Ca^{2+} appear to be well correlated in skeletal and cardiac muscle.

Smooth muscle myosin ATPase is not regulated in this way. In smooth muscle, the regulation of contractile activity occurs on the myosin filament itself. One of the components of the myosin head, the myosin light chain, can be reversibly phosphorylated. Myosin light-chain kinase, an exquisitely Ca^{2+}-sensitive enzyme, is one of several enzymes that phosphorylate the myosin light chain. After membrane depolarization or hormonal activation, smooth muscle cell Ca^{2+} rises, the myosin light chain becomes phosphorylated, and a contractile force develops.[18] In tracheal smooth muscle, there is a close relationship between the level of intracellular Ca^{2+} and myosin light-chain phosphate content; moreover, this relationship is invariant for several hormonal agonists and a Ca^{2+} ionophore. In response to a variety of agonists, light-chain phosphate content also correlates well with the initial shortening velocity of vascular smooth muscle strips.[19] Thus, it seems likely that contraction is initiated by a rise in the cell Ca^{2+} content that leads to activation of the myosin light-chain kinase, an increase in light-chain phosphate content, and the development of tension.

Unfortunately, this straightforward model of smooth muscle contraction cannot explain all aspects of the smooth muscle contractile response. Several types of experiments have shown that the relationship between intracellular Ca^{2+} and light-chain phosphate content can be dissociated when the two variables are measured and compared after hormone action versus membrane depolarization. More important, the relationship between intracellular Ca^{2+} and contractile force in vascular smooth muscle is not unique. In rat aortic smooth muscle, norepinephrine caused contraction at considerably lower Ca^{2+} levels than did ionomycin, a Ca^{2+} ionophore.[19] In fact, contraction in response to low concentrations of norepinephrine was found in the absence of demonstrable rises in the cell Ca^{2+} content.[19] As mentioned earlier, the activation of protein kinase C by phorbol esters causes contraction of vascular smooth muscle without raising the cell Ca^{2+} content measurably. Even more surprising is the finding that carbachol (a contractile agonist) and isoproterenol (a smooth muscle relaxant) both raised the Ca^{2+} levels equally in tracheal smooth muscle strips.[20]

The role of Ca^{2+} in determining vascular tone is even less clear when considering the tonically contracted vascular smooth muscle cell. After the initial development of a contractile force, the cell contractile system enters the "latch" state, in which tension is maintained despite a greatly diminished rate of cross-bridge formation and adenosine triphosphate use.[18] Because hypertension is probably due to tonic increases in smooth muscle tone and not to transient increases, this latch state is of great importance in understanding hypertension. Yet, remarkably little is known about how this state of contraction is maintained. What is known is that during maintained contraction, cell Ca^{2+} and myosin light-chain phosphorylation levels actually fall to basal or near-basal levels. Recent evidence in molluscan smooth muscle shows that the "catch" state, analogous to the latch state in mammalian smooth muscle, is maintained with cell Ca^{2+} at its basal level.[21] Moreover, relaxation of the catch state involves no change in cell Ca^{2+} concentration. Thus, latch states appear to be maintained by increasing the sensitivity of the contractile machinery to Ca^{2+} or, alternatively, by a Ca^{2+}-independent mechanism. Much more needs to be learned about the maintenance of these smooth muscle latch states before we can understand the maintenance of vascular tone.

In summary, Ca^{2+} is probably not the sole actor in the contraction of vascular smooth muscle cells. At the least, some agents, like norepinephrine, appear to increase the cell Ca^{2+} concentration and to also increase the sensitivity of the contractile mechanism to Ca^{2+}. The data do not have to be stretched far to suggest that Ca^{2+}-independent modes of contraction may also exist. Thus, models of hypertension are not forced to include increased cell Ca^{2+} content as the basis for the defect. Rather, in some persons, hypertension may be due to an altered sensitivity of the vascular contractile system to Ca^{2+} or even to Ca^{2+}-independent processes.

Some Possible Future Directions

Where should we now turn in the quest for a pathophysiologic basis for essential hypertension? Abnormalities in ion transport, as discussed, may yet hold the key to understanding the disease, but the missing links in this theory are still significant. Rather than discussing all other potential avenues for research in essential hypertension, I will limit my discussion to three areas that appear to hold promise for the future. The first is the existence of local renin-angiotensin systems in the vasculature and other tissues, the second is control of vascular tone by the endothelium, and the last is the role of smooth muscle cell hypertrophy in hypertension.

Local Renin-Angiotensin Systems

The role of the circulating renin-angiotensin system in the control of blood pressure has long been appreciated. More recent evidence indicates that the components of the renin-angiotensin system are produced locally in several tissues other than the kidney. Renin or angiotensin produced by these local systems may influence the blood pressure without ever reaching the circulation.

As long ago as the 1960s, there were indications that some renin is found in isolated blood vessels. While it is still not clear how much of this renin is produced locally and how much is trapped from the circulation, there is evidence that renin is produced in vascular smooth muscle cells,[22] and other evidence suggests that angiotensinogen and angiotensin-converting enzyme are also present in the vessel

wall. These data led to the hypothesis that angiotensin II produced within the vessel wall plays an important role in the control of blood pressure.[23] The existence of this system may explain why many hypertensive persons with normal or low levels of circulating renin respond well to converting-enzyme blockade.[24]

The renin-angiotensin system has also been found in other tissues, including the adrenal gland, brain, and placenta. A recent experiment using transgenic rats provides further support for the notion that locally produced renin and angiotensin may play a role in hypertension. Transfer of the mouse *ren-2* renin gene to rats caused severe hypertension in virtually all offspring expressing the gene product.[25] The hypertension was at least partially correctable with converting enzyme inhibitors. Surprisingly, circulating renin, angiotensin I, and angiotensin II were all suppressed in these animals. Of the tissues examined, the adrenal gland showed the highest levels of expression of the transgene. Thus, the adrenal gland may be another site where the renin-angiotensin system can influence the blood pressure without entering the circulation.

The Endothelium and Vascular Tone

Newly discovered vasoactive substances produced by the endothelial cell may also play a crucial role in the development of hypertension.[26] These substances may act directly on adjacent smooth muscle cells and affect vasomotor tone without entering the circulation. An excellent example of this phenomenon is the endothelium-derived relaxing factor, discovered by Furchgott and Zawadzi in 1980.[27] This agent, whose chemical identity is probably nitric oxide,[28] is released from endothelial cells in response to a variety of hormonal and physical factors. Because the half-life of nitric oxide is so short (several seconds), it probably acts to relax only the subjacent vascular smooth muscle cells before becoming rapidly inactivated in the circulation. Although the precise role for endothelium-derived relaxing factor in either normal or disordered cardiovascular function is still not clear, its mechanism of action is of therapeutic importance because the nitrate vasodilators appear to act by the same cellular mechanism as endothelium-derived relaxing factor.

A potent endothelium-derived vasoconstrictor, endothelin, has also recently been discovered.[29] This 21-amino acid peptide, a close relative of the asp venom toxin, sarafotoxin 6B, is released from cultured mammalian endothelial cells by thrombin, increased intracellular Ca^{2+}, and possibly by physical forces acting on the cell surface. Like endothelium-derived relaxing factor, endothelin does not appear to circulate significantly, but rather may act directly on the subjacent vascular smooth muscle cell to cause contraction.

Hypertrophy and Hyperplasia of Vascular Smooth Muscle Cells

Arteries and arterioles from persons with hypertension have long been known to contain an increased mass of vascular smooth muscle cells. In some vessels, this is due to hypertrophy of existing smooth muscle cells, while in others it is due to an increased number of cells (hyperplasia).[30] Whether it be associated with hypertrophy or hyperplasia, increased DNA synthesis in vascular smooth muscle cells is a prominent early feature of all forms of hypertension (Figure 3).[31] Although hypertrophy of blood vessels is often thought to be a cellular response to elevated pressures, there is considerable evidence that DNA synthesis can occur before the increase in pressure in some experimental models. For example, Carlier and associates found that DNA synthesis peaked at four days after one-kidney, one-clip hypertension was induced, long before the maximal blood pressure is reached.[32] Over the next two to three weeks, DNA synthesis fell towards control levels. Loeb and colleagues also found that DNA synthesis preceded the onset of hypertension in the two-kidney, one-clip model.[33] Thus, cell proliferation may play a crucial role in maintaining hypertension that is established by a wide range of causes.

What is the stimulus to hypertrophy or hyperplasia of vascular smooth muscle cells in hypertension? While this question has still not been answered, several possibilities have clearly emerged as the result of recent research on the biology of platelets, endothelial cells, and vascular smooth muscle cells themselves. These possibilities include a direct effect of wall stretch on cell growth, circulating mitogenic factors, the release of mitogenic factors by endothelial cells or platelets, and autocrine or paracrine regulation of growth by the smooth muscle cell itself.

Increased wall tension appears to play a role in the development of vascular hypertrophy in hypertension. In several experimental models, it has been found that a reduction of the blood pressure by various means will reduce or reverse the vascular hypertrophy. Stretch has been found to greatly enhance the production of a variety of extracellular matrix components in vascular smooth muscle.[34] Regional blood flow may also be a determinant of vascular wall thickness. Thus, physical factors that normally play a role in the modeling of vessel thickness may cause pathologic changes when the blood pressure becomes abnormally high.

Humoral factors involved in the development of hypertension could also exert a direct influence on the growth of vascular smooth muscle cells. In general, it has been difficult to separate the direct effects of humoral factors from those caused by hypertension itself. There is some evidence for a role of renin and angiotensin in vascular hypertrophy. Plunkett and Overbeck found that in coarctation hypertension, vascular hypertrophy was demonstrable in a normotensive bed below the level of the coarctation,[35] but there is as yet no general agreement on this point. Angiotensin does exhibit growth factor activity against cultured vascular smooth muscle cells, but it is probably not a potent mitogen. On balance, the role of renin and angiotensin in the development of vascular hypertrophy is probably limited.

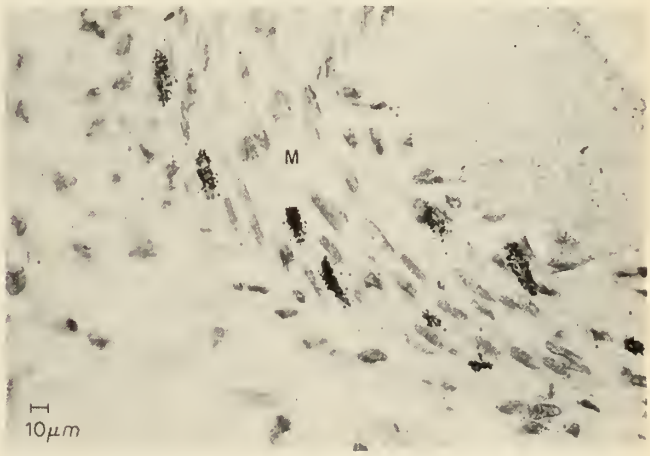

Figure 3.—The distribution of ^{3}H-thymidine is shown in medial smooth muscle cells of a small muscular artery from a rabbit with hypertension induced by coarctation of the aorta. DNA synthesis is demonstrated in smooth muscle cells throughout the thickness of the media. After autoradiography, slides were stained with hematoxylin and eosin (from Bevan[31]).

Other circulating factors could also play a role in the development of vascular hypertrophy. Catecholamines stimulate the proliferation of vascular smooth muscle cells,[36] and innervation by sympathetic nerves appears to be an important trophic factor in blood vessels. Serotonin is also a potent mitogen in vascular smooth muscle cells.[37] Thus, any of various circulating factors could play a role in the development of vascular hypertrophy.

New information suggests that local factors in the vascular wall play perhaps an even more important role than humoral factors in the control of smooth muscle cell proliferation. Local damage to the endothelial cell layer can lead to the activation of platelets with the release of platelet-derived growth factor, epidermal growth factor, serotonin, and transforming growth factor-β, all of which have mitogenic activity. Prostaglandins and thromboxanes may also play a role in the proliferative response. Endothelial cells themselves can be stimulated to release mitogenic factors, including the B chain of platelet-derived growth factor, fibroblast growth factor, and endothelin. Both platelet activation and endothelial damage are prominent early features of hypertensive damage to the vascular wall. Thus, factors produced by these highly reactive cells are likely to play a role in the pathogenesis of vascular hypertrophy.

Last, the vascular smooth muscle cell may respond abnormally in the hypertensive state. The smooth muscle cell is capable of producing growth-promoting (platelet-derived growth factor, insulin-like growth factor I, and interleukin 1) and -inhibiting (heparin) substances. Thus far, little is known about what regulates the synthesis of these substances in vivo. An abnormal in vitro proliferation of smooth muscle cells from spontaneously hypertensive rats is well documented, however.[38] In part, this increased proliferation may be due to a hyperresponsiveness to growth factors. Thus, there is the possibility that hypertension could be induced or maintained by a primary smooth muscle abnormality.

The foregoing discussion is neither an all-inclusive critique of the existing theories of the pathogenesis of hypertension nor a clairvoyant vision of future research in the field. I have tried to show that substantial arguments can be built against some of the existing major theories for the pathogenesis of hypertension and that an infusion of new thinking is needed. Only time and more hard work will reveal the answers in this exciting field.

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Human Obesity
Exploding the Myths

Discussant
DAVID S. WEIGLE, MD

This discussion was selected from the weekly Grand Rounds in the Department of Medicine, University of Washington School of Medicine, Seattle. Taken from a transcription, it has been edited by Drs Paul G. Ramsey, Associate Professor of Medicine, and Philip J. Fialkow, Professor and Chair of the Department of Medicine.

(Weigle DS: Human obesity—Exploding the myths. West J Med 1990 Oct; 153:421-428)

DAVID S. WEIGLE, MD*: Several misconceptions about obesity have hampered health care for the obese in recent years. Although the popular press and diet faddists have contributed to these misconceptions, the medical profession has often failed to provide a balanced view of the physiology of body weight regulation and the health hazards of obesity. Four commonly held beliefs underlie much of the confusion in this area. The first is that one's body weight is not a physiologically regulated variable but, rather, is set by acquired food habits and conscious or unconscious desires. A corollary of this misconception is that by choosing the right diet, a person could set his or her body weight to any desired level without incurring adverse health consequences in the process. A third misconception is that weighing more than a certain tabulated standard constitutes a sufficient health hazard in all persons that efforts to lose weight (usually by diet) should be undertaken. Finally, it is not commonly appreciated that body shape, which reflects the location of the dominant fat deposits, may have a much more important influence on a person's health than his or her overall weight. To develop rational guidelines for dealing with obese persons, it is important to address these four misconceptions.

Body Weight Regulation

Although a large body of empiric evidence argues convincingly that body weight is a regulated variable, it is useful to consider two general observations bearing on this issue. The first is that in most people body weight is either stable after adolescence or increases slowly over the lifespan.[1-3] Fox, whose average self-reported weight varied by less than 1.4 kg (3 lb) over a 19-year period, suggests that the mean annual weight gain of most Western populations is no more than 0.23 kg (½ lb) per year.[1] This degree of weight stability implies a precise match between energy intake and energy expenditure over prolonged periods. Even an 83.6-kilojoule (20-kilocalorie) excess in daily energy intake, the caloric content of a single soda cracker, would result in a 0.9-kg (2-lb) per year rate of weight gain. This precision in balancing daily energy intake and energy expenditure would be difficult to achieve on a purely volitional basis. It is more reasonable to postulate that energy balance reflects the operation of a physiologic regulatory, or homeostatic, mechanism.

Several excellent studies of body weight inheritance provide a second argument for body weight regulation. Studies of monozygotic and dizygotic twins suggest that a large portion of the variance in body weight among different family members is genetic in origin.[4,5] To elucidate whether this apparent inheritability of body weight is genetic or reflects the shared environment of family members, Stunkard and co-workers examined the body weights of Danish adoptees who had been separated from their biologic parents shortly after birth.[6] They found that the body weights of the adoptees correlated more closely with the weights of their biologic parents than with those of the foster parents in whose home the adoptees were raised. A direct explanation for these observations would be that one or more critical peptide molecules whose level(s) are determined by definable genes are in some way responsible for a person's body weight.

The usual body weight that a person maintains without conscious effort may be referred to as his or her "set point" weight. As weight deviates from this set point, restorative forces begin to operate to return the person to the set-point weight.[7] An increase in weight leads to increased energy expenditure and decreased appetite, whereas a decrease in weight leads to decreased energy expenditure and increased appetite. The power with which these restorative forces operate depends directly on the degree to which a person's weight has varied from the set point. On a day-to-day basis, the operation of these forces may be unnoticeable, whereas after a binge of holiday eating or the fasting associated with a transient illness, a person may experience pronounced satiety or hunger. Those in whom the restorative forces operate strongly experience relatively little variation in their daily or weekly body weights. Persons with a weaker regulatory response have greater weight fluctuations. It is important to note that both normal-weight and obese persons experience the same restorative changes in appetite and energy expenditure after a sufficient change in body weight. Thus, the regulatory system operates independently of the factors that actually determine the set point.

The set-point theory of body weight regulation is based on a large body of empiric evidence, only a small portion of which can be presented here. Considering appetite first, the work of Sims and associates showed that overfeeding normal-weight persons sufficiently to cause an 8% to 10% increase in body weight led to marked sensations of satiety or even nausea.[8] The satiety, and consequent suppression of voluntary food intake, observed by Sims and colleagues persisted until the body weight of each experimental subject returned to its previous baseline value. Overfeeding obese

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ABBREVIATIONS USED IN TEXT

BMI = body mass index
CHD = coronary heart disease
CT = computed tomography
HDL = high-density lipoprotein
NIH = National Institutes of Health
V:S ratio = ratio of visceral to subcutaneous fat

persons to cause a significant deviation above baseline weight leads to a similar decrease in appetite (R. Leibel, MD, Rockefeller University, oral communication, November 1989). The extreme increase in appetite that occurs with fasting to a subnormal weight in nonobese persons has been extensively documented by Keys and co-workers in a study of experimental semistarvation.[9] The intense hunger and preoccupation with food experienced by the subjects of this study persisted throughout the refeeding period until the baseline body weight was again achieved. The similar increase in appetite that occurs when obese persons lose weight by dieting contributes to the difficulty in maintaining weight loss experienced by reduced-obese persons.

The effects of deviations from set-point weight on energy expenditure also have been studied extensively. As early as 1902 Neumann recognized that body weight did not increase indefinitely despite the ongoing consumption of calories in excess of baseline weight maintenance needs.[10] Neumann reasoned that at body weights sufficiently above baseline, energy requirements were increased such that the excess calories were no longer stored as body fat. Sims and associates noted a similar leveling off of subjects' body weights despite the ongoing feeding of a caloric level significantly above baseline requirements.[8] Various other studies have shown that in both normal-weight and obese subjects, energy expenditure increases progressively as weight deviates above the set point for each person.[11-14] This increased energy expenditure, much of which occurs in the compartment of the resting metabolic rate, acts to limit further weight gain.

When food consumption is reduced such that body weight falls below the set point, both normal-weight and obese persons have a reduction in resting and total daily energy expenditures.[15-18] Leibel and Hirsch demonstrated this homeostatic energy-conserving response with an obese subject group that had an average weight of 152 kg and a daily energy requirement of 15.3 MJ (3,651 kcal).[15] After reducing to a mean final weight of 100 kg, the energy requirement of this group fell to 9,075 kJ (2,171 kcal) per day, which was actually less than the 9,530-kJ (2,280-kcal)-per-day requirement of a group of lighter control subjects at their mean baseline (set point) weight of 63 kg. Geissler and colleagues made similar observations in a group of reduced-obese and normal-weight women studied at several different levels of activity.[16]

To better define the mechanism of energy conservation with weight loss, we did two studies of obese and reduced-obese persons.[19,20] In the first of these studies we confirmed that the weight-stabilizing caloric intake—a measure that reflects total daily energy expenditure—and the resting metabolic rate of a group of men and women decreased substantially with stable weight reduction.[19] The resting metabolic rate, which was proportional to fat-free mass at baseline weight, showed exactly the same relationship to the reduced fat-free mass after weight loss. A second study of obese men before and after weight loss was designed to determine the degree to which the reduced energy cost of physical activity at the lower body weight contributed to the energy savings of the reduced-obese state.[20] To this end, five obese men were placed on an energy-restricted diet until a mean 23% weight loss was achieved. A matched group of five subjects on the same diet wore a specially tailored vest into which flat lead weights could be placed. The subjects were weighed twice a week, and weights were added to the vests at each weighing session to exactly compensate for body weight lost on the diet to that point. Subjects wore the vests under their usual clothing for 16 hours per day. A comparison of the energy expenditures of the two subject groups before and after weight reduction revealed that weight replacement, by keeping the energy cost of physical activity comparable to baseline values, cancelled about half of the fall in energy expenditure of the vest-wearing group. Control subjects had a 3,829-kJ (916 kcal)-per-day (29% of baseline) fall in energy expenditure, whereas weight-replacement subjects had only a 1,689-kJ (404 kcal)-per-day (12%) decrease. Thus, the reduction in energy expenditure that occurred with a 21% to 23% weight loss represented both a metabolic adaptation and a roughly comparable biomechanical energy savings.

These observations regarding the operation of the body weight regulatory system can be incorporated into a model as shown in Figure 1. The central nervous system, responding to both internal and environmental appetite cues, initiates eating. Food intake occurs until signals arising largely from the gastrointestinal tract are interpreted by the central nervous system to produce the subjective experience of satiety.[21] This short feedback loop principally regulates the size of a meal. On a longer term basis, the ingestion of calories in excess of immediate needs leads to an expansion of the adipose mass. A signal or signals, the level of which is proportional to the excess adipose store, then increase in the circulation and augment the experience of satiety elicited by the gastrointestinal factors in the central nervous system.[22,23] The average meal size would consequently be reduced until the adipose mass returns to its baseline value. As the adipose mass expands, the total body weight increases, leading on a biomechanical basis to a partially compensatory increase in activity-related energy expenditure. The increase in fat-free mass that accompanies increasing adiposity results in a higher resting energy expenditure. Circulating factors proportional to the adipose mass could also modulate energy expenditure directly. The net effect of decreasing food consumption and increasing energy expenditure would be to reduce the adipose mass towards its baseline value. When a deficient caloric intake leads to contraction of the adipose mass, a regulatory response opposite to that discussed above tends to restore the adipose reserve to baseline.

Although alternatives to the scheme diagrammed in Figure 1 can be envisioned, this model shows that body weight is set at the point of balance of the various feedback loops that regulate the adipose mass. The genetic influence on body weight could be mediated primarily through differing levels of expression of the long-term circulating satiety factor(s) or its receptor in the central nervous system. Persons who express the active factor or its receptor at low levels would have to gain relatively more adipose tissue until the decrease in appetite and increase in energy expenditure are sufficient to result in energy balance. Body weight regulation would then occur around this elevated set point. The critical circulating factor or factors proposed in Figure 1 remain to be discovered. Porte and Woods have suggested that insulin, the circulating level of which is proportional to

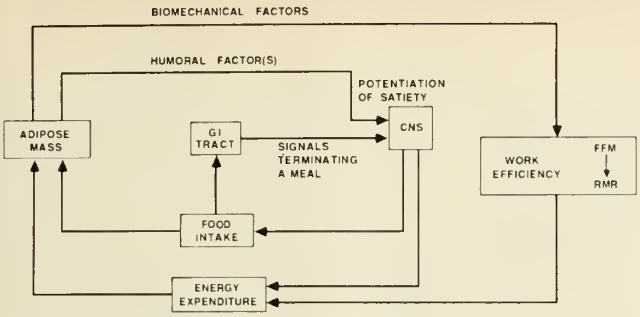

Figure 1.—The schema is of a model for the body weight regulatory system. See text for explanation. CNS = central nervous system, FFM = fat-free mass, GI = gastrointestinal, RMR = resting metabolic rate

body fat content, could be an important long-term physiologic satiety factor.[24] The recent discovery of adipsin, however, suggests that adipose tissue itself could secrete peptides that function to regulate body weight.[25] This is an area of intense current research interest.

Several arguments have been offered against the existence of body weight regulation.[7] It has been suggested that the notable variability of body weight among different persons is inconsistent with a real homeostatic mechanism. This argument is no more compelling than the suggestion that interindividual differences in blood pressure disprove the existence of blood pressure regulation.[7] Body weight set point, if determined by the level of expression or activity of one or more gene products, would be expected to vary in a population unless the resultant phenotype led to impaired reproductive success. The slow upward drift in adiposity that occurs with normal aging has also been offered as an argument against the existence of body weight regulation. This objection may be addressed by comparing the energy imbalance implied by a typical yearly weight gain with the total caloric flux occurring over a similar period of time. Thus, a yearly weight gain of 0.2 kg[1] represents an energy excess of only 7,524 kJ (1,800 kcal) per year. This figure constitutes less than 0.2% of a typical yearly intake of 1 million calories. This "failure" of body weight regulation could simply reflect an age-related decline in the synthesis of a critical regulatory factor (Figure 1), much as cardiac and renal performances decline with normal aging. Finally, the observation that body weight can be influenced by the hedonic qualities of food has been cited as evidence against a regulatory system. Again, this observation has no more relevance than the observation that a high salt intake can lead to an increased blood pressure.[7] Were it not for the usual stability of body weight, the transient increase in weight occurring after a binge of holiday eating would go unnoticed. The degree to which indiscretion in eating affects a person's weight depends only on the strength of the counterregulatory responses in that person and his or her discomfort in the face of satiety. As a population exposed incessantly to a surfeit of prepared and convenience foods, we probably always exist close to a maximal tolerable weight above the set point.

The Dubious Value of Diet Alone in Managing Obesity

If a person's body weight were set by habit or desire, then voluntary dietary energy restriction should provide a "cure" for obesity. The long-term maintenance of weight loss achieved through diet alone, however, is poor in most persons. Drenick and Johnson reported that only 7 of 121 morbidly obese subjects who had lost weight on a regimen of fasting followed by semistarvation remained below their starting weights at a mean of 7.3 years' follow-up.[26] Pavlou and co-workers, and other investigators who have employed less draconian diets, have reported comparably poor long-term results.[27] This general outcome of dietary therapy is not surprising in light of the strength of the body weight regulatory system discussed above. The task of keeping a person's weight considerably below its set-point value through dietary energy restriction is comparable to attempting to maintain a significantly elevated serum osmolarity through voluntary restriction of free water intake. Only persons with incredibly strong will power or the ability to tolerate physical discomfort are likely to be successful in this attempt to defeat a homeostatic mechanism. The degree of physical and emotional discomfort induced by dietary energy restriction depends primarily on the degree to which body weight deviates below its set point.[9]

Our national preoccupation with dieting might be excusable if dissatisfaction were the only adverse consequence of this rather ineffective approach to the treatment of obesity. Dieting carries certain risks, however, that must be considered when making individual therapeutic or public health recommendations. The use of severely energy-restricted or unbalanced diets has been associated with deficiency syndromes, arrhythmias, and sudden cardiac death.[28,29] Fortunately, the collagen hydrolysate diets that were associated with many of these cardiac complications have been removed from the market.[29] Even balanced energy-restricted diets invariably lead to chronic fatigue, impaired concentration, cold intolerance, and malaise as the body weight drops progressively below its set point. These symptoms are associated with a decrease in fat-free mass and objective decreases in muscle strength and endurance.[27] Impaired peripheral conversion of thyroxine to triiodothyronine with dietary energy restriction may also contribute to these symptoms. Welle and Campbell have shown that the replacement of triiodothyronine in subjects consuming a low-caloric diet partially restores their energy expenditures towards normal.[30]

Several adverse psychological outcomes of dieting are important. Because attempts to maintain weight loss achieved through diet usually fail, many persons put themselves through repeated cycles of dieting. Repeated failures with diets may lead to low self-esteem and reinforce the erroneous notion that the person is to blame for his or her own obesity. Frustration with energy-restricted diets may lead a person to ignore more useful dietary guidelines aimed at preventing hyperlipidemia, diabetes mellitus, and colonic diseases. Obsession with dieting on a population basis may contribute to the increasing incidence of anorexia nervosa and bulimia in this country.[31] Finally, unrealistic expectations of dietary therapy for obesity by health care providers may delay the institution of effective pharmacologic therapies for the obesity-associated conditions of diabetes mellitus, hypertension, and hyperlipidemia.

Ernsberger and Haskew have proposed that some of the health complications that have been associated with obesity may actually be caused by energy-restricted diets or the acute realimentation that follows dietary failure.[32] These authors cite, among other studies, the epidemic of hypertension and congestive heart failure following the Siege of Leningrad in 1942 as a large-scale demonstration of the danger of refeeding after caloric deprivation.[33] The pronounced peripheral edema that often develops in patients with anorexia nervosa during treatment also illustrates the potential harm of cycles of energy restriction and refeeding. This sodium and fluid retention is presumably due to enhanced renal sensitivity to mineralocorticoids that develops

during caloric restriction and the abrupt increase in the insulin level that follows realimentation.[34] On the basis of limited studies in animals and humans, it appears that cycles of weight loss and regain may lead to a reduction in daily energy requirements.[35,36] This enhanced metabolic efficiency would, in turn, promote further weight gain with each new cycle of dieting. Although this potential adverse effect of "yo-yo" dieting is both plausible and worrisome, more research is needed to verify these preliminary observations.

The set-point theory of body weight regulation has been viewed with great pessimism precisely because it implies the futility of dieting.[37] A more optimistic alternative view, which has ample precedent in medical research, is that only when a problem is reduced to its physiologic roots is it possible to find a meaningful solution. With molecular biologic techniques, the critical regulatory factor(s) postulated to exist in Figure 1 is likely to be identified long before the complex psychodynamics offered by some as an "explanation" for obesity are unraveled. Perhaps the best course to take while awaiting a more fundamental biochemical insight is to recommend the use of energy-restricted diets as a treatment of obesity only in situations where the potential benefits clearly exceed the risks. Such situations might include ventilatory failure associated with obesity or when preparing a morbidly obese person for an elective surgical procedure. As will be discussed later, a general public health recommendation for weight reduction through dieting cannot be supported strongly with existing data.

The proper food choices and regular aerobic exercise have at least as much to offer in the treatment of obesity as dietary energy restriction. Exercise programs, either used alone or in combination with mild caloric restriction, have been shown to enhance the successful long-term maintenance of weight loss.[27] Regular exercise may lower the set point for body weight regulation.[7] Certainly when the body weight is dropped below the set point by exercise, the total daily energy expenditure remains appropriate for the new weight, in contrast to the notable fall in energy expenditure observed when the same amount of weight is lost by diet alone. Additional benefits of regular exercise include improved cardiovascular fitness, a greater sense of well-being, and improvements in blood pressure, carbohydrate tolerance, and lipid profile. Perhaps most important is the growing evidence that exercise is associated with increased longevity in a variety of study populations.[38,39]

The Overstated Health Hazards of Moderate Obesity

Compared with the health hazards of smoking, hypertension, diabetes mellitus, and certain hyperlipidemias, the adverse health consequences of moderate obesity are relatively mild.[40] Nevertheless, the panel of the 1985 National Institutes of Health (NIH) Consensus Development Conference stated that "weight reduction should be recommended to persons with excess body weight of 20% or more above desirable weights in the Metropolitan Life Insurance Company tables."[41] Given the potential adverse consequences of dieting discussed earlier, it is important to examine the data on which such a sweeping public health recommendation is based.

The Metropolitan tables, which have been published at intervals since the early 1940s, are an attempt to relate mortality experience to body weight in the insured population. An "optimal" (lowest mortality) weight is tabulated for three frame sizes in each height and sex category. Although the concept of an optimal weight may be sound in principle, several problems make the use of these tables as a cornerstone of public health policy risky.[42] Because most of the data on which the tables are based reflects the experience of white upper- and middle-class men, the tables may not be generalizable to the American population as a whole.[42] The average follow-up period of one of the central data bases from which the tables were formulated was only 6.6 years.[42] It is impossible to judge the effect of other important variables, such as cigarette smoking, on the tabulated data.[42] Furthermore, no explicit definition of frame size was built into the data bases from which the tables were drawn, and the important effect of subject age on the relationship between body weight and mortality is not incorporated into the tables at all.[43] Finally, tables of optimal weight for height give no information as to the rate at which mortality increases as weight deviates from the optimum. A steeply increasing relationship between mortality and weight would justify a more aggressive public health approach to obesity than would be justified by a less pronounced relationship.

Figure 2.—The graphs show the relative mortality for three age groups according to the body mass index (ratio of weight to height squared) (from Waaler[44]).

Several studies have shown that the curve relating body weight and mortality from all causes is U- or J-shaped.[43-45] Mortality increases with a deviation either above or below a particular weight that increases with age.[43] In the largest study of body weight and mortality to date, 1.7 million Norwegians aged 15 years or older were observed for ten years.[44] As shown in Figure 2 for three age groups enrolled in this study, risk ratios for overweight persons varied between only 0.9 and 1.8 over a wide range of a body mass index (BMI). These risk ratios are considerably less than those associated with smoking, hypertension, diabetes mellitus, and certain hyperlipidemias.[46] As described by Waaler, "the curves are very wide at the bottoms, indicating uncertainty in the determination of an optimum, or in other words that a rather extensive overweight is required to give an excess mortality of any importance."[47] The 20% overweight guideline for weight reduction suggested by the NIH Consensus Development Panel corresponds to BMI values in the range of 25 to 27 kg per m^2.[41] As shown in Figure 2, the increased mortality associated with this degree of overweight is inconsequential.

In the United States, an American Cancer Society study of 750,000 men and women produced data comparable to those obtained in the Norwegian study.[45] The U-shaped curve relating mortality and body weight for all subject ages combined was again rather broad, with a maximum risk ratio of about 1.9 for both men and women greater than 140% of average weight. For weight categories as high as 120% of average weight, mortality ratios remained less

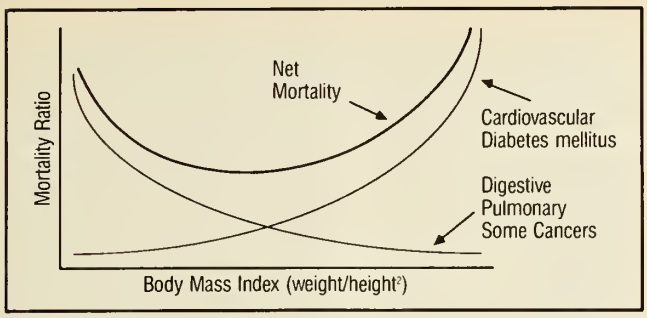

Figure 3.—The graph shows the origin of the U-shaped curve relating overall mortality to adiposity. Disease categories responsible for deaths at both low and high values of body mass index are noted.

than 1.2. It is important to note that in the American Cancer Society study, weights were expressed as percentages of the observed average weights rather than as percentages of ideal body weights. Because these weights were generally higher than those appearing in the 1959 Metropolitan tables, the risk ratios corresponding to the NIH Consensus Development Panel's treatment guidelines for obesity would actually be less than 1.2. On the basis of overall mortality data, it appears that general recommendations for the treatment of obesity should be targeted toward more overweight persons, particularly if treatment is ineffective or associated with its own morbidity.

As shown in Figure 3, the U-shaped curve relating body weight and mortality from all causes can be explained by the occurrence of distinct categories of disease at opposite extremes of body weight.[32,44,45] Deaths due to obstructive lung disease, peptic ulcer disease, stomach cancer, lung cancer, and tuberculosis tend to be more frequent at lower body weights, whereas cardiovascular, cerebrovascular, and diabetes-related deaths are more common in obese persons. The excess deaths occurring at low body weights are not simply due to the preexisting disease causing weight loss or the association between smoking and reduced body weight.[32] Given the incidence of cardiac death in developed countries, the important public health question about obesity relates to whether an increased body weight constitutes a true risk factor for cardiovascular morbidity and mortality.

Univariate studies of the relationship between body weight and cardiovascular end points support the association of obesity with cardiovascular disease. Obesity, however, is also associated with hypertension, diabetes mellitus, hypertriglyceridemia, hyperinsulinemia, and low levels of high-density lipoprotein (HDL) cholesterol. Because each of these factors has been implicated as a risk factor for coronary heart disease (CHD), it is difficult to determine whether obesity is an independent risk factor for cardiovascular disease. It has been suggested that the tight association of all of these variables, along with the favorable response of hypertension and blood glucose and lipid levels to body weight reduction, makes the independence of obesity as a risk factor for CHD irrelevant. Counterarguments to this somewhat nihilistic point of view include the poor long-term outcome of most attempts to treat obesity, the morbidity associated with energy-restricted diets, and the more effective pharmacotherapy available for the "metabolic complications" of obesity. Perhaps most important, a better understanding of the relationship between body weight and coronary artery disease could lead to a more fundamental understanding of the causes and prevention of atherosclerosis.

Several studies have employed multivariate analysis in an attempt to identify any independent contribution of obesity to CHD morbidity and mortality. The results of seven of these studies are summarized in Table 1 according to an increasing duration of follow-up. The Japan-US study, which was designed principally to differentiate environmental and genetic influences on CHD risk factors, somewhat surprisingly found obesity to confer an independent risk for CHD after only two years of follow-up in the American cohort.[48] This result was not confirmed in the mainland Japanese cohort, perhaps because of the low incidence of obesity among these men. The Walnut Creek (California) Contraceptive Drug Study, one of the few large studies of cardiovascular disease in women, found a relative risk of 2.2 for myocardial infarction as a function of obesity.[49] This result was barely significant (χ^2 3.1) after adjusting for smoking, alcohol use, blood pressure, cholesterol level, and gallbladder disease. The Gothenburg, Sweden, and seven countries studies of men found no independent association between obesity and coronary heart disease despite follow-ups of 13 and 15 years, respectively.[50,51] Only subjects in the 40- to 59-year age range were enrolled in those studies, however. The Los Angeles Heart Study found obesity to confer a risk for CHD independent of serum cholesterol levels and blood pressure after 15 years of follow-up.[52] This effect of obesity was restricted to men younger than 40 years at enrollment. Because blood glucose, triglyceride, and HDL-cholesterol levels were not measured in the Los Angeles study, it is impossible to determine whether obesity conferred its risk through unfavorable changes in these variables. In the Manitoba study, 26 years of follow-up were required to show a significant effect of obesity on CHD morbidity and mortality.[53] As in the Los Angeles study, obesity was a risk factor only in men younger than 39 at

TABLE 1.—*Is Obesity an Independent Risk Factor for Coronary Heart Disease?*

Source	*Study Population or Location*	*Patients, No.*	*Sex*	*Initial Age, yr*	*Follow-up, yr*	*Answer*
Robertson et al, 1977[48]	Japanese and	1,963	♂	45-68	5	No
	American	7,705	♂	45-68	2	Yes
Petitti et al, 1979[49]	Walnut Creek, Calif	16,759	♀	18-54	6.5	Borderline
Larsson et al, 1984[50]	Gothenburg	792	♂	54	13	No
Keys et al, 1984[51]	Seven countries	11,579	♂	40-59	15	No
Chapman et al, 1971[52]	Los Angeles	1,859	♂	20-70	15	Yes*
Rabkin et al, 1977[53]	Manitoba	3,983	♂	15-64	16	No
					26	Yes*
Hubert et al, 1983[54]	Framingham, Mass	2,252	♂	28-62	12	No
		2,818	♀	28-62	26	Yes

♂ = male, ♀ = female

*Effect seen only in subjects younger than 40 years at enrollment.

enrollment. Because the only covariables included in the Manitoba study were age and blood pressure, little can be concluded about the independence of obesity as a coronary artery disease risk factor. Finally, after 26 years of follow-up, the Framingham study found obesity to confer a risk for CHD outcomes that was independent of age, cholesterol levels, systolic blood pressure, smoking, left ventricular hypertrophy, and glucose intolerance in both men and women.[54] Again, the adverse associations of body weight were most apparent in subjects younger than 50 at enrollment.

Several explanations may be offered for the conflicting data regarding obesity as an independent risk factor for coronary artery disease. First, obesity could simply be a rather weak factor predisposing to atherosclerosis. This possibility is suggested by the appearance of an association between obesity and CHD outcomes only in subjects who were enrolled at earlier ages and followed for periods of 20 years or more. Andres recognized this important modulating influence of age on the risk associated with obesity and formulated a set of optimal weight for height tables in which age and height rather than sex, frame, and height are the index variables.[43] These tables indicate that in younger subjects, who would have exposure to any harmful effects of obesity for longer time periods, the weight associated with the lowest mortality is lower than in older subjects. A second explanation for the apparent ambiguity of obesity as a CHD risk factor could be that obesity is associated with a more important, but as yet unproved or unrecognized, atherogenic condition. Hyperinsulinemia may be one such condition.[55] Finally, as will be discussed, obesity may consist of several subgroups, some of which are associated with accelerated atherosclerosis and some of which are not.

The Importance of Body Fat Distribution

Vague in 1956 was the first worker to divide human obesity into either android (central) or gynoid (lower body) subtypes.[56] He noted that premature atherosclerosis, diabetes, gout, and uric calculous disease were more commonly associated with the android type of obesity. Vague attributed both android obesity and its complications to overactivity of the pituitary-adrenal axis. These early observations have been confirmed and refined by a large number of subsequent studies, only a few of which can be considered here.

In the Honolulu Heart Program, 7,692 men of Japanese ancestry were observed for as long as 12 years to determine the relationship between central body fat distribution and the occurrence of definite CHD (nonfatal myocardial infarction and CHD-related death).[57] A single measurement of subscapular skinfold thickness was used as an index of centrality, and the body mass index was used as a measure of overweight. When the data were analyzed by tertiles, subscapular skinfold thickness was found to be a stronger predictor of CHD than was the BMI. Within any tertile of subscapular skinfold thickness, the relationship between the BMI and CHD was not significant. Risk factors that showed a positive correlation with the subscapular skinfold thickness included total cholesterol, blood glucose, and triglyceride levels and blood pressure status. After adjustments were made for these risk factors as well as age, BMI, and the use of cigarettes, the relationship between subscapular skinfold thickness and CHD remained significant (relative risk for the highest versus the lowest tertiles of skinfold thickness, 1.5; 95% confidence intervals, 1.1 to 2.1). The significance of this independent association between central body fat distribution and definite CHD is particularly impressive because the subscapular skinfold thickness reflects overall body fat content almost as well as it reflects central fat distribution. A variety of studies that have used other techniques to measure regional body fat also suggest that the most overweight persons tend to be the most centrally obese. This relationship between degree of overweight and central obesity in study populations could certainly explain the apparent association between obesity and CHD outcomes noted in Table 1. As the authors of the Honolulu Heart Program report note, "The focus of attention on the independent predictive ability of obesity may be misplaced."[57(p823)]

TABLE 2.—*Percentage Probabilities of Myocardial Infarction and Death From Any Cause in Relation to Tertiles of Body Mass Index and Ratio of Waist to Hip Circumference**

Tertiles of Waist to Hip Ratio	Tertiles of Body Mass Index (Weight/Height²) Lowest	Middle	Highest
Myocardial Infarction			
Lowest	0.9	0.0	0.0
Middle	1.1	0.9	1.5
Highest	3.8	0.0	3.5
Death			
Lowest	7.6	2.5	1.0
Middle	4.7	4.7	4.7
Highest	7.0	5.2	6.3

*From Lapidus et al.[58]

The Gothenburg longitudinal study of 1,462 women reached conclusions similar to those of the Honolulu Heart Program in a female population.[58] In this 12-year study, central body fat distribution, as reflected by an elevated waist-to-hip ratio, was more closely associated with a variety of cardiovascular end points than was the BMI or the sum of skinfolds (another index of general adiposity). As shown in Table 2, tertiles of increasing waist:hip ratio correlated with an increasing probability of either myocardial infarction or death in most tertiles of BMI. In contrast, within any tertile of the waist:hip ratio, there was no increase in the probability of either of these end points with increasing BMI. When a multivariate analysis was used to remove the confounding effects of age, BMI, smoking, total cholesterol and triglyceride levels, and systolic blood pressure, the association between the waist:hip ratio and myocardial infarction remained significant. As in the Honolulu study, the occurrence of the highest waist:hip ratios in the most overweight persons would have led to an apparent independent association between the BMI and CHD if considered out of context.

Recent studies employing computed tomography (CT) have further defined the relationship between central obesity and factors contributing to an increased CHD risk. Fujioka and co-workers determined the ratio of visceral to subcutaneous fat (V:S ratio) in 46 obese subjects by means of CT at the level of the umbilicus.[59] The mean V:S ratio of the subject group as a whole was 0.4. A V:S ratio of greater than 0.4 (but not the BMI or duration of obesity) identified subjects who were more likely to have non-insulin-dependent diabetes mellitus and higher values of fasting blood glucose, plasma glucose area after oral glucose loading, total cholesterol, and triglycerides when compared with those of subjects with a V:S ratio of less than 0.4. When multiple-regression analysis was used to remove any confounding effect of BMI and age, the correlation between the V:S ratio and the plasma glucose area, total cholesterol, and triglyceride levels remained significant.

Peiris and associates measured abdominal visceral fat by CT and total body fat by hydrostatic weighing of a group of 33 obese premenopausal women.[60] In multivariate analyses, visceral fat, as compared with total fat, accounted for twice the percent variance in blood pressure, insulin response to an oral glucose load, and the ratio of HDL to total cholesterol measured in the study subjects. After adjusting for visceral fat, there was no significant association between these CHD risk factors and the total body fat. In contrast, the association between visceral fat and risk factors remained significant after adjusting for total fat. The waist:hip ratio correlated less strongly with CHD risk factors than did visceral fat.

The balance of evidence suggests that the excess abdominal visceral fat of persons with central obesity predisposes to CHD both through traditional risk factors and other factors, such as hyperinsulinemia, that were not considered in the Honolulu and Gothenburg studies. Björntorp has hypothesized that the greater lipolytic activity of abdominal visceral adipose tissue may mediate the adverse metabolic effects of central obesity.[61] This enhanced lipolytic activity appears to be due to a higher ratio of β- to α_2-adrenergic receptors and lower insulin sensitivity of the adipose tissue depots that drain into the portal circulation.[62-64] A greater delivery of free fatty acids to the liver would tend to promote the synthesis of very-low-density lipoproteins and create insulin resistance with resultant hyperinsulinemia.[61] These derangements could lead to hyperlipidemia and diabetes mellitus in many persons. Hyperinsulinemia is also associated with hypertension, but the pathogenetic link between these two conditions is less clear.[61]

Human Obesity—What to Do Until More Answers Are Available

Although the cause or causes of human obesity are not yet known, several conclusions may be drawn from the evidence summarized above. Perhaps most important is the observation that obesity is not a disorder of body weight regulation. Most obese persons regulate their weight appropriately about an elevated set-point weight. This set point appears to be strongly influenced by the person's genotype. As hypothesized in Figure 1, diminished expression of, or a reduced ability to respond to, a circulating satiety factor, which signals the long-term status of the body's energy reserve to the central nervous system, may constitute the genetic lesion, resulting in a high set-point weight in some obese persons. This hypothesis is encouraging in that it implies a discrete defect that should be approachable through the techniques of molecular biology. The discouraging news, however, is that energy-restricted diets are a physiologically unsound means to achieve weight reduction. Energy restriction calls into play strong counterregulatory responses both in appetite and energy expenditure that almost invariably act to restore a reduced-obese person to his or her set-point weight. Exercise as a primary approach to weight loss may circumvent this counterregulatory response to some degree, while conferring other important health benefits.

The health hazards of moderate obesity may have been overstated to the American public. The mortality risk ratios of 1.1 to 1.2 that accompany BMI values in the 30- to 35-kg-per-m^2 range probably do not justify the widespread application of a therapy as ineffective and likely to cause adverse physical and psychological effects as the energy-restricted diet. To a large degree, obesity confers an enhanced risk for CHD through the associated risk factors of hypertension, diabetes mellitus, hyperlipidemia, and possibly hyperinsulinemia. Any significantly increased CHD risk conferred independently by obesity appears to be restricted to younger centrally obese persons.

Until a more detailed understanding of the physiology of body weight regulation is attained, several guidelines for the management of obesity seem justified:

- Target therapeutic efforts to younger patients with elevated waist-to-hip ratios (>0.95 in men, >0.85 in women).
- Dietary instruction should emphasize correct food choices as equal in importance to caloric restriction. Keep dietary weight loss goals moderate.
- Emphasize regular exercise in the therapeutic program for obese persons.
- Do not withhold pharmacologic therapy for the obesity-related disorders of hypertension, hyperglycemia, and hyperlipidemia in the face of unrealistic expectations for sustained weight loss.

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Editorial Comment

Is Obesity Due to a Heritable Difference in 'Set Point' for Adiposity?

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Adipose tissue lipid content reflects the long-term balance between energy intake and output. Small positive imbalances in this relationship over long periods of time can result in the accumulation of large amounts of excess fat. An adult human ingests about 214,000 kilojoules (900,000 kilocalories) per year. The caloric content of adipose tissue is about 1.7 kJ (7 kcal) per gram. Thus, a cumulative "error" in the balance of energy intake and output of as little as 5% could result in accumulations (or losses) of 6 kg of adipose tissue per year. Body weight or composition in "free-feeding" humans generally does not show yearly fluctuations of this magnitude. In fact, body weight remains remarkably stable over long periods of time, even in the absence of conscious efforts to control it, and experimental perturbations of body weight are met by resistive metabolic forces tending to return body composition to its starting state.[1,2] Observations of this sort have been taken as evidence for the existence of a "set point" for body fatness, though alternative possibilities[3] have been suggested.

Is there a set point for fatness in humans or animals? If so, what is regulated (fat cell size, number, total fat mass), what is sensed (a metabolite of fat, a peptide secreted by fat), and where is the sensor (brain, liver)? Although many provocative experiments have been done that probed these possibilities, the answers to these questions are not known.

A number of animal models support the idea of a set point for adiposity. Specific regions within the brain regulate food intake and play a role in metabolic efficiency.[4] The latter influence may be mediated by autonomic efferents.[5] Although it is clear that anatomically diverse regions of the central nervous system participate in feeding behavior, the function of the ventromedial and lateral aspects of the hypothalamus provides a good paradigm for the existence of such sites within the brain.[6] Ablative lesions of the ventromedial and lateral aspects of the hypothalamus result in respective increases and decreases in body fat that reflect coordinate changes in both food intake and energy expenditure.[7] The fact that such lesions cause alterations in both food intake and energy efficiency has suggested that these regions of the brain may subserve a set-point function, rather than controlling a single efferent or afferent limb (such as food intake or energy efficiency) of the regulatory process. Animals with lesions in these parts of the central nervous system generally regulate their weights normally about the new set points created by ablative procedures. This phenomenon again supports the notion of a central regulator of adiposity per se.[7]

Genetically obese rodents include autosomal dominant (Yellow and Adipose mice), recessive mutations (obese, diabetic, fat, and tubby mice; fatty rats), and "polygene" obese mice such as the New Zealand Obese.[8] The existence of these mutations indicates that in a mammalian system, obesity or diabetes mellitus, or both, may result from a single gene mutation. Human syndromes such as the Prader-Willi and Bardet-Biedl syndromes indicate, likewise, that a purely genetic basis may exist for some (very rare) forms of human obesity.[9-11]

The rodent mutations are particularly intriguing because they represent potential access to single genes regulating energy homeostasis that generate phenotypes (hyperphagia and increased energy efficiency) closely resembling those seen in obese humans. Similar phenotypes are produced by mutations occurring on four different chromosomes in mice, suggesting that these genetic loci may all subserve a single regulatory pathway.[12] Evidence in support of this idea comes from parabiosis (shared blood flow) experiments in mice that suggest that the *ob* (chromosome 6) locus codes for a circulating satiety factor for which the *db* (chromosome 4) locus product is the receptor.[13] An additional important phenotypic aspect of these animals is the longer survival of heterozygotes *(ob)* during a total fast,[14] a finding consistent with a putative selective advantage conferred by a "thrifty" genotype.[15]

The severity of the diabetes that develops in these mice is highly dependent on the background strain on which the gene is engrafted. Thus, *ob/ob* on the C57BL/6J background produces obese mice with transient insulin resistance, which is compensated by pancreatic β-cell hypertrophy. On the C57BL/KsJ background, homozygosity for *ob* results in severe diabetes with ultimate pancreatic failure (β-cell atrophy) and shortening of the lifespan.[16] A wide variation in phenotype for a single mutant allele, due to modulating effects of the background genome, suggests that a few allelic variants of these genes, segregating in the human population, might be sufficient to account for the heritability of obesity and diabetes.

Efforts to quantify the heritability of obesity in humans are confounded by problems that derive from the (apparent) polygene contributions to phenotype, the powerful effects of environmental circumstance on the penetrance of whatever gene(s) may be involved, and the experimental use of phenotypes (such as weight or weight-for-height constructs) that do not make the fine distinctions (such as body composition, energy efficiency, hedonic factors in food intake) necessary to identify differences that may define subsets of causes. A variety of studies, including those

(Leibel RL: Is obesity due to a heritable difference in 'set point' for adiposity? West J Med 1990 Oct; 153:429-431)

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of twins and adopted children, find that between 5% and 80% of the variance in adiposity is attributable to genotype.[17-20] A portion of the wide range of values is due to the failure to distinguish total transmissible variances (which includes genotype plus environmental interactions) from pure, additive genetic effects.[19] The genetic influence on body shape (distribution of fat) appears to be as strong as or stronger than that for total body fat.[19] Strong genetic contributions have also been shown for fat deposition during overfeeding and for energy expenditure at low levels of exercise.[21] Experiments in animals suggest that early nutritional experiences may influence the penetrance of obesity-producing genes (such as in Zucker rats) in older animals,[22] and studies in humans suggest qualitatively similar effects of the prenatal environment.[23,24] In the aggregate, however, studies of feeding practices and rates of weight gain in infancy have not suggested an important role for either of these factors in the risk of obesity in childhood or adolescence.[25]

In the case of the control of body composition, it is clear that the phenotype is a changeable reflection of complex interactions of genotype and environment. Industrialized cultures, with their ready access to calorically dense foods and the diminished need for physical exertion, are optimal environments for the maximum expression of genetic predispositions to the maintenance of high levels of body fatness.

In this issue of the journal, Weigle takes positions that are implicitly influenced by some of the physiologic and genetic considerations described above.[26] Several specific points concerning his arguments may be made:

- What is the proper approach to the management of moderate degrees of obesity? As indicated by Weigle's discussion, there is considerable debate about the health risks of mild to moderate adiposity—that is, 110% to 130% above "desirable" body weight. The U- or J-shape of the relationship between body weight (or body mass index [BMI]) and all-cause mortality demonstrated by various epidemiologic studies is largely an artifact of the failure to control for one or more of the following variables: cigarette smoking; inappropriate factoring out of the biologic effects of obesity that confer mortality as intervening variables (hypertension); and a failure to control for weight loss due to subclinical disease.[27] When these are considered, it appears that "minimum mortality occurs at weights at least 10% lower than US average weights," and that even mild degrees of obesity confer an increased mortality risk.[27] This argument has resurfaced in a paper published since Weigle wrote his review. In a large eight-year prospective study of 115,886 nurses 30 to 55 years of age, even mild degrees of obesity were associated with a 20% to 30% increased coronary artery disease risk; there was no broad plateau in lower portions of the function relating BMI to coronary artery disease risk. Women with the lowest BMIs (<21) had the lowest risk of coronary events, and rates increased for all quintiles with higher BMIs. Thus, there did not appear to be a "safe" level of mild adiposity in this study.[28]
- It has been difficult to show an important adverse metabolic consequence of obesity separate from those conveyed by this condition's effects on blood pressure and carbohydrate and lipid homeostasis. Whether such an influence exists is of biologic interest but probably of little therapeutic significance. The medical consequences of obesity can, in most instances, be treated by weight reduction, medication, or a combination of the two. Given the apparent adverse consequences of even modest degrees of obesity, it seems important to counsel prevention, remembering that childhood obesity is not necessarily a good predictor of obesity in adulthood[29] and that an overaggressive restriction of calories in a child can restrict the growth of lean tissues.[25] In adults, conscientious efforts at weight control should be recommended for virtually all obese persons—perhaps with special attention to those showing evidence of adverse medical consequences of their excess adiposity. The likelihood of success is clearly greatest in those with the least severe obesity. In instances where the maintenance of reduced weight proves impossible, attention should be shifted to pharmacologic treatment of the medical consequences of obesity because they convey the major portion of the risk attributable to obesity.
- Body shape (distribution of fat) conveys a substantial part of the medical risk associated with obesity. Careful studies by Kissebah and collaborators have documented a reduction in hepatic insulin extraction in persons with upper-body obesity leading to peripheral hyperinsulinemia and diminished peripheral insulin sensitivity.[30] This group has also shown evidence of a role for circulating androgens in the preferential deposition of intra-abdominal fat.[31] Body shape changes little following weight reduction in adults, so that "apples" and "pears" tend to become reduced versions of the same fruit.[32,33] Despite this, weight reduction leads to improvement in these medical risk factors, suggesting that absolute abdominal adiposity is more important than is relative (waist:hip ratio) adiposity in this regard. For that reason, normative data should be developed relating the abdominal circumference to a power function of stature—comparable to the body mass index (weight: height^2)—rather than relying on the waist:hip ratio, which does not give as direct a measure of absolute abdominal adiposity.
- The enhanced energy efficiency of formerly obese persons apparently contributes to the high recidivism rate to obesity.[34,35] It is not yet clear to which metabolic compartment(s) this enhanced efficiency may be attributed. It appears, however, that physical activity (total motion, mechanical efficiency, or both), rather than resting metabolic rate or the thermic effect of feeding, is the most likely candidate.[36] Whether these differences precede—and may therefore be causal of—obesity is not known. Studies in both infants[37] and adults[38] suggest that low energy output precedes the onset of obesity. The existence of such enhanced energy efficiency cannot, however, be the complete answer. Still unexplained is why energy intake does not simply decrease to match the lower energy output, thus preventing the imbalance of intake versus output that leads to obesity. This discordance of food intake and energy output highlights the critical interaction of behavior and metabolism in the pathophysiology of obesity and indicates the conceptual error inherent in efforts to define obesity as exclusively a disorder of either behavior or metabolism.[39]

The set point does not seem to encode a specific level of food intake or energy output but rather an amount or proportion of fatness. Thus, obese and never-obese persons regulate normally about their "usual" body compositions, making adjustments in food intake and energy expenditure that are appropriate to the maintenance of that degree of weight. Intake and output become matched once a specified level of fat storage is achieved.[38] An understanding of the biomolecular basis for this regulatory process may ultimately enable its developmental or pharmacologic manipulation. Meanwhile, conscientious, lifelong attention to diet and levels of physical activity must be employed to defeat

the biologic drive to high levels of adiposity and to enhance the quality and length of life in those to whom nature may have dealt a high "set point."

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Epitomes

Important Advances in Clinical Medicine

Physical Medicine and Rehabilitation

The Scientific Board of the California Medical Association presents the following inventory of items of progress in physical medicine and rehabilitation. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers, or scholars to stay abreast of these items of progress in physical medicine and rehabilitation that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Physical Medicine and Rehabilitation of the California Medical Association, and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Lumbar Stabilizing Exercises for the Nonoperative Treatment of Disc Lesions

Although only a small percentage of patients with low-back pain have clear evidence of a herniated disc as the cause of their pain, these patients account for a majority of the lumbar spine operations performed in the United States, and the number of such operations in this country has increased substantially over the past ten years. The herniated lumbar disc has been known for 50 years to be a cause of sciatica and back pain, yet, until recently, little has changed in the clinical approach and perspectives on treatment and pain mechanisms in this disorder. In patients with a primary complaint of leg pain and neurologic signs in a single-level distribution, a "success" rate of 72% to 90% could be achieved with a single-level discectomy. Thus, in the past, most of the patients with a lumbar herniated disc and radiculopathy were treated with varying amounts of bed rest and analgesic medication for two to six weeks, at the end of which time they were considered to be surgical candidates if their symptoms had not reached a tolerable level. Moreover, those patients with a disc extrusion were referred to surgical therapy more quickly as this lesion was considered by itself to be an indication for such. Recent advances in our understanding of the biochemistry of lumbar disc herniations, the natural history of lumbar disc extrusions treated nonoperatively, and the successful role of a specific exercise training program have expanded and improved the nonoperative treatment available for these patients.

Herniated disc material in the past was thought to generate symptoms solely by virtue of pressure on spinal nerves. Recent biochemical studies of herniated disc material from patients undergoing discectomy for radiculopathy disclosed high levels of an inflammatory enzyme, phospholipase A_2, within the herniated material at its interface with the epidural space. As the enzyme responsible for the liberation of arachidonic acid from cell membranes, phospholipase A_2 has been shown to play a role in numerous pathologic states of inflammation. Its activity is considered to be the rate-limiting step in the production of prostaglandins and leukotrienes. As a source for the local production of prostaglandins and other inflammatory intermediates, it is therefore likely that herniated discs exert a chemical as well as mechanical influence on spinal nerve roots.

The use of stabilizing exercises for the nonoperative treatment of herniated lumbar discs has recently been shown to be as effective as surgical treatment, based on previously published results from surgical studies using the same type of patients. Consecutive patients with a primary complaint of leg pain and a disc herniation documented by magnetic resonance imaging (MRI) or computed tomography whose condition failed to improve with six weeks of passive measures were treated with an aggressive specific exercise program. Most of these patients had neurologic weakness equal to grade 1 on the manual muscle testing scale of the Medical Research Council. The program centered around the use of stabilizing exercises to train patients to limit rotational and flexion forces across the lumbar spine in all activities. The epidural administration of corticosteroids was used to control the inflammatory component in those patients whose pain prevented them from advancing in the exercise program. The program included the functional training of stabilizing techniques for all recreational and occupational activities. Most of the patients (93%) returned to work and to most preinjury recreational activities.

Included among the nonoperatively treated patients were patients with extruded lumbar discs and those who sought a second opinion regarding surgical treatment recommended as the only answer to their pain and disability. Among these groups, a success rate of 90% and 87%, respectively, was achieved. The patients with extruded disc herniations were then observed for as long as three years. Follow-up MRI studies were done to evaluate the presence of perineural fibrosis and the size of the disc herniation. Almost all of the disc fragments were smaller, and the majority had completely resolved. In no instance was there any sign of perineural fibrosis or fragment migration. An adequate control of inflammation coupled with a specific lumbar stabilization training program aimed at functional activity replaces the need for an operation in most patients with a herniated lumbar disc.

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Falls in the Elderly

FALLING REPRESENTS A MAJOR HEALTH and socioeconomic problem with an estimated cost of $6 billion per year in the United States. It is the leading cause of death due to accidents among those 75 years of age or older. For every fall leading to death there are about 20 that result in hip fractures, accounting for at least 185,000 fall-related hip fractures per year. These fractures result in 40% of admissions to nursing homes. In the community among independently functioning older adults, one of three persons aged 65 years or older falls at least once a year.

Most falls do not result in serious injuries, but such episodes often lead to an increased fear of falling among the elderly, with a loss of self-confidence and a less active lifestyle.

Factors that contribute to falling include impairments of the vestibular, visual, musculoskeletal, or proprioceptive systems that may be the result of intrinsic physiologic aging phenomena or deconditioning, cardiovascular or neurologic disorders, and impaired balance iatrogenically induced by medication. In a one-year prospective study of the relative risk of these potential hazards among 336 community-residing elderly aged 75 or older, the most important risk factors distinguishing the 32% who fell at least once were the use of sedatives (relative risk [RR] 3.1), previous falls (RR 2.5), lower extremity disabilities (RR 2.4), and a near-vision loss of 20% or more (RR 1.7). The risk of falling increased linearly with the number of disabilities.

The result of efforts directed toward reducing the incidence of falls is thus far inconclusive. It has been shown, however, that the severity of injuries resulting from falls can be reduced by educating community-residing older adults on how to recognize and exercise caution in hazardous situations such as sudden glare, dark halls, and carpeted stairs with worn tread.

Additional strategies for preventing falls may include exercise to improve strength and mobility, health education with nutrition guidelines to retard bone loss, and medication counseling.

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Spinal Stenosis—What's New?

EXPERIMENTAL EVIDENCE regarding the pathophysiology of lumbar spinal stenosis has further defined the process in the central canal. The primary problem is venous stasis and spinal nerve root and dorsal root ganglia engorgement and edema. A low pressure is responsible for this and is rapidly reversible with the restoration of venous circulation, correlating well with neurogenic claudication. The spinal nerve root also is susceptible to entrapment in the lateral lumbar spinal canal, but no research has been done yet on the critical dimensions of this canal.

Central canal diameters considered to be critical are less than 130 mm^2, with a normal range of 200 to 340 mm^2. The cauda equina is protected by the dura until the central canal is narrowed to 75 mm^2. Venous stasis in the root occurs at a 25% constriction with no structural histopathologic damage and no clinical neurologic deficit. A 50% narrowing produces weakness and demyelination. With 75% constriction, severe root injury and cauda equina damage occur.

Structural changes do not determine the source of pain, and advances in electrophysiologic diagnosis have been made with dermatomal somatosensory evoked potential (SEP) testing. This allows a precise localization of the root level of intermittent neurologic dysfunction with only conduction block present. Root dysfunction due to venous stasis and transient conduction block is accurately detected by stress-SEP testing. Testing is done after a patient has walked until symptoms are produced. The sensitivity of this test is greater than twice that of electromyography, but polyneuropathy is not as well defined as with electromyography. Somatosensory evoked potential testing allows a rapid noninvasive test to differentiate neurogenic from vascular intermittent claudication.

Precise neurodiagnostic testing serves as a guide to accurate surgical decompression. Intraoperative SEP testing can assure adequate root decompression. Neurophysiologic testing provides a measure of root function that cannot be intimated from radiologic structural assessments.

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Somatosensory Evoked Potentials in Cord and Root Diseases

SOMATOSENSORY EVOKED POTENTIALS (SEPs) for the stimulation of selected nerve trunks or areas of skin contained within dermatomes may be used for segmental localization of spinal cord impairment or for nerve root assessment. Segmental SEPs are scalp recordings taken over the appropriate topographic areas of the postcentral gyrus. An impairment is localized by selecting for stimulation those nerve trunks or areas of skin within dermatomes that are associated with specific nerve roots or cord levels under question.

Data on normal subjects have been reported for several segmental levels. Most studies have focused on lumbosacral or cervical level inputs. Our laboratory has collected normative data for cervical, thoracic, and lumbosacral dermatomes.

We have demonstrated the diagnostic usefulness of segmental SEPs by comparing the effectiveness of dermatomal SEPs and electromyograms in patients with lumbar spinal stenosis. Of 26 patients who met all criteria after computed tomography, myelography, or both, 25 (96%) had abnormal SEPs bilaterally. By comparison, only 15 (59%) showed bilateral abnormalities by electromyography, suggesting that segmental SEPs are more likely to detect the root levels that are involved in spinal stenosis. A similar percentage of abnormality (95%) by dermatomal SEPs was reported recently in a study of 20 patients with disc disease and lumbar

canal stenosis. These percentages are higher than those reported in earlier studies of lumbar radiculopathy, probably reflecting that the efficacy of segmental SEPs in identifying root abnormalities associated with spinal stenosis is greater than with disc disease.

In segmental cervical level analysis, both nerve trunk and dermatomal SEPs may be used. Some studies have reported that SEPs are helpful in diagnosing root disease and identifying sensory levels in quadriplegia, although not all would agree as to their use. It is probably reasonable to say that at the cervical level SEPs serve best as an adjunct to other electrodiagnostic studies.

At the thoracic level, it was found that in two thirds of 37 patients studied, the level of conduction impairment was better located with thoracic dermatomal SEPs. Although more study of segmental SEPs needs to be done at the thoracic level as well as cervical and lumbar levels, these SEPs hold promise for a useful, noninvasive test of cord and nerve root function.

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Objective Measures of Lumbar Strength

Back pain is the most frequent cause of limited activity and lost time from work for persons younger than 45. About 80% of people will suffer at least one attack of significant back pain in their lifetimes, and 90% to 95% will recover within three months. The small percentage of patients who do not recover account for more than 80% of the medical costs for all patients with back pain. As back pain becomes chronic, the results of treatment decline dramatically. After two years less than 10% of patients will return to work or to moderately strenuous activities no matter what treatment is given.

Rest, medication, passive symptomatic physical therapy, and surgical therapy—in properly selected cases—are common early treatments. For patients for whom these treatments initially fail, however, prolonged bed rest, increased doses of medication, more hot packs, and a second operation have all been shown to aggravate rather than alleviate chronic pain.

Epidemiologic studies showed a tenfold increase in back injuries for the least fit firefighters compared with the most fit of that same group. A study using isometric strain gauge testing of strength showed that the incidence and severity of work-related lifting injuries were directly related to a worker's relative strength compared with the job requirements. In 1981 the National Institute of Occupational Safety and Health published guidelines for materials handling that included strength testing for workers who were asked to lift more than light loads close to the body.

The first isokinetic (constant speed) devices for low back testing and strengthening reached the market five years ago. Normative data on trunk flexor-extensor strength in normal persons and in those with back injuries became available. Studies showed that a population with chronic low back pain had significant deconditioning in back extensors and flexors and that a ten-week treatment program using strengthening exercises, gym equipment, and simulated work activities could objectively increase strength and return workers to their original jobs. A control group treated with standard methods had half the success and twice the long-term costs. Objective measures of the body's ability to perform certain functional tasks were found to be more helpful than the patients' subjective reports of pain.

Subsequent studies have confirmed that patients with and without operations showed substantial benefits from education, training, and strengthening when the pretreatment deficits could be objectively quantified and when progress during treatment could be followed objectively. The initial isokinetic testing is most commonly combined with a half- to two-day tolerance testing of a simulated work environment (physical or functional capacity evaluation). Subsequent testing during and after treatment gives a clinician useful information to guide treatment and to determine a return to work or vocational rehabilitation status.

Isokinetic strength measurement is not in any way diagnostic of the underlying pathologic condition. Deficits in strength and endurance in patients with no definable disorder may be similar to those in patients with severe disease. The data are reproducible, with most patients showing 10% to 25% variability during subtests of a single test. Patients can be trained, however, to accurately reproduce submaximal effort. Inconsistent test results (varying more than 25%) are seen in patients with submaximal effort, elaborated pain drawings, elevated scores on the Minnesota Multiphasic Personality Inventory, "ratchety" give-way weakness, or inconsistent straight-leg raising (positive Waddell's signs). Patients with a notable functional overlay often refuse conditioning programs and do not show incremental objective increases in strength.

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Self-Defense for People With Disabilities

Because disabled persons are often perceived to be powerless, helpless, and unable to protect themselves, they are often targets for violent crime, including homicide, assault, rape, and robbery. Recent studies have documented that elder abuse is most widespread among elderly people who have physical or mental disabilities, that about 100,000 disabled women annually are victims of rape, that wife abuse is an especially widespread problem in the deaf community, and that there is a significantly increased incidence of physical and sexual abuse of children with developmental disabilities.

Although people with disabilities may have certain limitations, such as vision, hearing, speech, or mobility, they are usually able to develop other capabilities and to draw on available resources to protect themselves. Underestimating a patient's capabilities can be as devastating as overesti-

mating them. Therefore, physicians should encourage persons with handicaps not only to be aware of their vulnerability but also to take sensible precautionary steps for their own safety.

Self-defense training for disabled persons is becoming increasingly available through medical rehabilitation centers, community crime prevention groups, and martial arts classes. Three major types of defense are prevention, psychological defense, and physical defense. Prevention occurs through precautions to reduce vulnerability at home, work, school, on the street, while traveling, and through social encounters. Along with prevention, psychological preparation is important—thinking through what to do in a given situation, knowing the options, assessing one's abilities and limitations, avoiding looking or acting like a victim, acting assertive and confident, and identifying resources in the community for the development of preventive measures. Surprise is an assailant's advantage; that advantage can be reduced by practicing, both mentally and physically, what to do in a physically threatening situation. As for physical defense, there are two main theories of how to respond to an assault: some say talk, some say fight. Talk can be used to delay until an opportunity for help or escape is evident. Physical resistance against a firearm is never recommended. Otherwise, current consensus favors being prepared and practicing for an assault situation so that the first two or three moves can be sufficiently devastating to provide time to escape, seek help, or sound an alarm. With this as a goal, self-defense training for wheelchair users and persons with other disabilities has already proved effective.

Some rehabilitation centers offer classes in martial arts such as judo, jujitsu, kung fu, and karate. The practice of routines of self-defense develops the mind to react instantly to threatening situations and teaches persons not to try to stand firm and oppose an attack but to apply the principles of physics and kinesiology to use an opponent's force to convert an attack into a defeat. Although the best defense remains the avoidance of risky situations, if ever a disabled person is under physical attack, martial arts offer an effective means of training for self-protection and survival.

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Neuropharmacologic Interventions in Traumatic Brain Injury

ADVANCES HAVE OCCURRED in the past decade in the rehabilitation of patients with traumatic brain injury that have altered the approach to this condition. Treatment has been extended, moved out of hospital settings, and directed toward cognitive, behavioral, and social as well as physical deficits. Neuropharmacologic management is a second and complementary innovative approach that offers additional benefits to survivors of brain injury. Nearly all investigation in the past of the pharmacologic treatment of traumatic brain injury was concerned with the acute phase of the injury. The goal of such treatment has been to prevent immediate complications, to minimize the severity of the initial injury, or to manage severe or emergency behavioral disturbance (violence). Neuropharmacologic methods had not been developed to manage the irreducible chronic behavioral and cognitive losses of brain impairment.

With a recognition that behavioral and cognitive deficits of brain injury constitute the greatest barrier to maximal independence, the possibilities of neuropharmacologic methods to ameloriate these chronic deficits have become evident. The goal of such treatment is to suppress undesirable behavior and augment adaptive behaviors. Traumatic brain injury produces specific—but to a large extent unknown—neurophysiologic (including neurotransmitter) disturbance. This disturbance contributes to a variety of functional deficits, including frontal, temporal, and information processing. Theoretically, it seems rational to administer agents that act to counter transmitter deficits or imbalances, remediating the internal milieu of the damaged brain, and thus to some extent "normalizing" brain activity.

It is appropriate to consider these psychopharmacologic approaches in at least four clinical situations or syndromes. These are decreased arousal, hyperarousal and agitation or aggression, affective disturbance, and cognitive impairment. Stimulants and dopaminergic agonists are most often reported useful for underaroused patients. A large and growing list of potentially useful agents is available for hyperaroused or aggressive patients, including the high-potency neuroleptic agents (traditionally the agent of choice for this indication), lithium carbonate, β-blockers, anticonvulsants (especially carbamazepine), tricyclic (and other) antidepressants, stimulants, and antianxiety agents. For affectively depressed patients, antidepressant drugs are appropriate. The diagnosis of depression in this organically impaired population is a challenge, however, as patients' internal mood states may be inaccessible because of aphasia, agnosia, or frontal impairment. Biologic signs of depression such as psychomotor retardation; sleep, sexual, and appetitive disturbance; and weight loss may all reflect direct deficits of the neurologic injury itself, thus confounding diagnosis. Secondary mania and hypomanic states also clearly result from brain injury and appear to respond to the use of lithium and carbamazepine.

Cognitive disorders are the most common and important deficits in patients with traumatic brain injuries. Because impaired cognition is an almost universal consequence of brain trauma and because even modest gains could have tremendous functional consequences, further investigation is warranted of potential clinical benefits of agents such as stimulants, antidepressants, dopaminergic agonists, neuropeptides, and other drugs reputed to enhance cognitive activity, such as piracetam.

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Computer-aided Quantitative Analysis of Diagnostic Electromyography

Clinical electromyography (EMG) is extremely useful in evaluating patients with neuromuscular diseases. During that part of the study involving the examination of muscles with intramuscular needle electrodes, a physician engages in a dynamic, interactive process with a patient as the data are recorded. In conventional EMG, interpretation is subjective and the results are reported in descriptive terms.

Manual methods of EMG quantitation have existed for many years but have not been adopted into routine practice because the benefits are outweighed by the disadvantages of being tedious and time-consuming. In the past few years, however, with the availability of equipment with rapid digital processing capabilities, strong interest has developed in the quantitative analysis of needle EMG. Software programs have been developed that offer a range of possibilities in two broad categories of analysis, namely the quantitation of motor unit action potentials and the interference pattern. In analyzing the motor unit action potentials, the potentials are extracted from the ongoing EMG signal and any of the following variables may be measured—peak-to-peak amplitude, number of phases, number of turns, duration, rectified area within the defined duration, the ratio of area to amplitude, and firing pattern. Studies are usually done on low-threshold motor units recruited during low-level contractions, although some programs permit the extraction of action potentials at higher force levels. The simplest programs assist the operator by measuring the motor unit action potentials, but the electromyographer still must record and display the individual potentials. More advanced programs will extract, identify, and measure motor unit action potentials, providing considerable saving of operator time and effort. Automatic analysis of the interference pattern may include measurements of baseline crossings, peaks, turns, amplitude of deflections, turns-to-amplitude ratio, and the frequency spectrum of the signal.

Reference data recorded from normal subjects are available for some of these measures, especially motor unit action potential analysis at low efforts and analysis of the turns:amplitude ratio of the inference pattern. Comparable reference data for the other measures are being reported as more experience is gained with them. It is relatively easy for electromyographers to develop their own laboratory norms because the equipment has become standardized and the software easier to use.

The opportunity for easy quantitation of the EMG signal will influence the way electromyographers approach diagnostic EMG in those patients in whom pathophysiologic changes are most apparent on needle examination, such as those with generalized disorders (myopathies and denervating diseases). Conventional EMG examinations, performed by observation, analyzed subjectively, and reported descriptively, will remain acceptable practice in routine diagnosis. Automatic quantitation, however, allows a more detailed and thorough analysis of the pathophysiology of the disease process and hence a more valid basis for diagnosis. The severity of a disease process is quantifiable, and the presence of special or unusual features, such as mixed patterns in some patients with inflammatory myopathies, can be recognized. Quantitation of the EMG offers considerable advantage over conventional subjective EMG interpretation for detecting the progression of disease in follow-up studies.

Despite the technical advantages of computer-aided quantitative analysis, it is still not possible for a technician to independently record an EMG for the subsequent interpretation by a physician. On the contrary, EMG examination is now more demanding of physicians who must remain attentive to the details of the technique and the proper use of equipment. Computer-aided quantitative EMG analysis provides clinical electromyographers an additional array of specific procedures, any of which may be selected to enhance the diagnostic study in any given patient.

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Deep Vein Thrombosis in Patients With Spinal Cord Injury

Patients with acute spinal cord injury are highly prone to the development of deep vein thrombosis. Deep vein thrombosis delays rehabilitation, prolongs hospital stays, and hence increases the cost of care. Important complications are pulmonary embolism, which is often fatal, and the post-thrombosis syndrome with permanent swelling and edema in the leg. The factors contributing to the high incidence include stasis following paralysis and immobility, hypercoagulability of blood, tissue trauma, and infection. The risk is greatest in the first three months after injury and declines after six months. During the acute phase, an increase in the platelet responsiveness to collagen and an increase in the ratio of factor VIII antigen to factor VIII C has been reported.

The reported incidence of deep vein thrombosis in patients with spinal cord injuries has been decreasing during the past decade because of earlier admissions to hospital, better diagnostic methods, and aggressive prophylaxis or therapy, but it still remains in the range of 10% to 25%. Clinically, contrast venography remains the gold standard of definitive diagnosis, although radionuclide scanning is also an accurate means of diagnosis, has the added advantages of detecting pelvic vein thrombosis and active heterotopic ossification, and can be used on a limb with a cast.

A prophylactic regimen in current use includes fixed-low-dose subcutaneous heparin (5,000 units every 12 hours), adjusted-dose subcutaneous heparin to keep the activated partial thromboplastin time (PTT) at a desired level, low-dose warfarin sodium, pneumatic compression and aspirin, pneumatic compression alone, and functional electrical stimulation alone or in conjunction with any of the above. Fixed-dose subcutaneous heparin is the most commonly used regimen. It can reduce the incidence of calf vein thrombosis substantially compared with that in patients not given prophylaxis. The failure rate, however, for a fixed-dose regimen has been reported to be 10% to 31%. An adjusted-dose regimen aimed at maintaining the activated PTT (six hours after the evening dose) at 1.5 times the control value has reduced the incidence of deep vein thrombosis to 7%, but hemorrhagic complications occurred in 24% of the patients.

The current clinical approach of choice to prophylaxis

for deep vein thrombosis is to tailor the regimen individually, especially with regards to the dose type, route, and duration of anticoagulation. The flexible approach is guided by the degree of hypercoagulative risk present in each patient as assessed from the combined clinical and laboratory data. This includes the general risk factors, local condition of the limb, the period after injury, the degree of spasticity of the limbs, ambulation, infection, hemorrhagic risk, anticipated surgical procedure, previous history of thromboembolism, drug interaction, and the patient's compliance. Laboratory tests indicating hypercoagulability include a short activated PTT, a high-dose requirement for anticoagulation, a high fibrinogen value, and an increased level of fibrin degradation products. The dose of subcutaneous heparin is modified from Leyvraz and colleagues. If a patient is at a low risk, 5,000 units of heparin is given subcutaneously every 12 hours. The dose is increased until the activated PTT, determined just before the morning dose, reaches the upper limit of the normal range (37 to 40 seconds). If the total dose exceeds 20,000 units in 24 hours, the injections are given every 8 or even every 6 hours to avoid high blood concentrations of heparin. If the patient is at high risk and the total heparin requirements exceed 30,000 units a day, the heparin is given intravenously until the risk, heparin requirements, or both are reduced. High-risk patients are anticoagulated during perioperative periods. The anticoagulation regimen is not withdrawn simply at the end of an arbitrarily defined period—such as 8 to 12 weeks—but only when the patient is considered to be reasonably out of risk. An unresolved risk is covered with anticoagulation therapy on a long-term basis. Our experience with the use of this regimen shows a failure rate of less than 5% and no significant hemorrhage.

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Alerts, Notices, and Case Reports

A Case of Neuroleptic-Induced Laryngospasm

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AGENTS CAUSING DOPAMINE blockade are notorious for eliciting an extrapyramidal syndrome. Although neuroleptics are among the most widely used of these agents, other commonly used dopamine blockers can also cause this syndrome. These medications include antiemetics such as prochlorperazine and metoclopramide, sedatives including meperidine, and the antihypertensive drug reserpine.[1]

The extrapyramidal syndrome includes motor abnormalities such as dystonic reactions, akathisia, and tardive dyskinesia. Of these, a dystonic reaction is defined as an involuntary muscular spasm leading to an abnormal posture or grimace.[2] Dystonias may be generalized, focal, or segmental.[3] Focal dystonias affect the musculature in one of the following areas: the eyes (oculogyric crisis, blepharospasm), neck (torticollis), jaw (trismus), tongue, back (opisthotonos), or the larynx (laryngospasm).

The English-language literature on medication-induced dystonic reactions focuses primarily on the neuroleptic agents. These studies indicate that the prevalence rate of dystonic reactions among patients receiving these agents may be as high as 47%.[2] Men appear to be more frequently affected than women, and the incidence of adverse reactions seems to decrease with age.[4] Furthermore, the time of highest risk is documented to be during the first 72 hours of treatment.[5]

Collectively, the studies on neuroleptic-induced dystonic reactions are difficult to assess because of differing patient populations and the type of neuroleptic agent studied. Taking these variables into account, one important review of the literature implicates the use of the higher potency neuroleptics such as haloperidol and thiothixene as having a higher rate of dystonia.[4] In assessing the oral administration of high-potency neuroleptics and the appearance of dystonic reactions, another study found an average lag time of 15.5 hours for neuroleptic agents in general and 10.9 hours for haloperidol specifically.[6]

Although a wealth of literature exists on dystonia in general, descriptions of idiosyncratic, medication-induced laryngospasm and its treatment are relatively sparse. Laryngospasm is an extrapyramidal reaction resulting from acute spasmodic contractions of the laryngeal muscles.[5] Laryngospasm can present with spasmodic dysphonia,[7] mild respiratory difficulties, or outright respiratory distress with stridor leading to hypoxia and ultimately death.

One author has reported laryngospasm as a rare side effect of the intramuscular administration of high-potency neuroleptics in young men in their 20s and 30s that was responsive to the use of antiparkinsonian agents.[5] Except for one brief reference, there is little documentation of the course and treatment of medication-induced laryngospasm.

(Garcia MM, Mercer PR: A case of neuroleptic-induced laryngospasm. West J Med 1990 Oct; 153:438-439)

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Report of a Case

The patient, a 27-year-old man, was admitted for the first time to a psychiatric unit because of bizarre and threatening behavior. After an initial evaluation, a diagnosis of atypical psychosis was reached. Treatment with haloperidol was uneventful, and within 48 hours of his first dose the patient's bizarre behavior cleared. Before discharge, laboratory studies revealed the presence of phencyclidine hydrochloride in the urine.

Five months later the patient was readmitted to the same facility for the treatment of acute psychosis. He was agitated and required restraints and the administration of 5 mg of haloperidol intramuscularly along with 2 mg of benztropine mesylate. Because of the patient's condition, further information was unobtainable.

Within an hour after being administered the medications, the patient fell asleep and did not awaken for 11 hours. After noting that he was drooling excessively, the nursing staff requested an evaluation.

On examination, the patient was alert, cooperative, but restless and drooling. He was given 2 mg of benztropine mesylate intramuscularly. Within minutes a severe lingual dystonic reaction developed, accompanied by some difficulty breathing. The patient began to grasp at the anterior aspect of his neck as he gasped for air. This progressed to unmistakable stridor and perioral cyanosis. While the "code blue" team was called, the patient was given 25 mg of diphenhydramine hydrochloride intravenously. Within 30 seconds the respiratory crisis began to subside, resolving within two minutes. Over the next 24 hours, a regimen of diphenhydramine was given and neuroleptics were discontinued. A toxicology screen ruled out the presence of street drugs or other medications.

Discussion

Dopamine agonists, as well as several groups of medications, have been documented as successfully treating differing forms of dystonic reactions. These drugs include clonazepam, lorazepam, diazepam, diphenhydramine, and benztropine mesylate.[7-10] In assessing the efficacy of these agents, researchers concluded that intravenously administered benztropine mesylate showed the fastest mean improvement time and least sedating properties.[9]

Although studies cited attest to the efficacy of benztropine mesylate as prophylaxis against neuroleptic-induced dystonia,[4] it is noteworthy that the case described herein occurred despite its use.

This case represents an idiosyncratic reaction to a dopamine-blocking agent with which this patient had been successfully treated five months earlier, showing that a history of an uneventful response to these agents does not rule out the possibility of a near-catastrophic reaction with further use.

Dysphonia and respiratory difficulty may often accompany mild cases of laryngospasm. Considering the frequent misdiagnosis of dystonic reactions,[11] these are signs that, in a healthy young adult who has been recently treated with

dopamine-blocking agents, must arouse a suspicion of laryngospasm. The most important factors for the successful treatment of this dystonic reaction are early and accurate diagnosis.

The efficacy of initial treatment with 50 mg of diphenhydramine given intravenously followed by the discontinuation of the dopamine-blocking agent concurs with a previous report describing the use of diphenhydramine as effective.[5] When the half-life of the dopamine blocker is greater than that of either benztropine mesylate or diphenhydramine, it is advisable not only to discontinue the agent but also to continue with prophylactic coverage during the next 24 hours. We posit that the sedating effects of diphenhydramine may be of additional benefit in a patient who has suffered a near-catastrophic event.

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Coexistence of Primary Biliary Cirrhosis and Sarcoidosis

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PRIMARY BILIARY CIRRHOSIS, a progressive inflammatory and cholestatic liver disease, may involve extrahepatic sites such as the lung (Table 1). Interstitial lung disease including usual interstitial pneumonitis,[1-3] lymphocytic interstitial pneumonitis,[4] and organizing pneumonitis with the CREST syndrome [calcinosis cutis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia][5] occur in patients with this disorder. Bronchoalveolar lavage abnormalities have been described in these patients without evidence of lung disease.[6] In addition, lung parenchymal granulomas have been found, which raises the possibility of either sarcoidosis or primary pulmonary granulomas with primary biliary cirrhosis.[2,3,7] Herein we describe the case of a patient with this disorder and coexistent sarcoidosis. While corticosteroid therapy resulted in a resolution of the pulmonary lesions, the liver disease progressed, requiring transplantation.

(Leff JA, Ready JB, Repetto C, et al: Coexistence of primary biliary cirrhosis and sarcoidosis. West J Med 1990 Oct; 153:439-441)

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Supported in part by National Institutes of Health Fellowship Training Grant HL-07085.

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Report of a Case

The patient, a 40-year-old woman, had pruritus and abdominal bloating develop five months before admission. Also noted was hyperpigmentation over all body surfaces, and jaundice appeared three weeks before admission.

She reported a positive tuberculin skin test during pregnancy (age 25), but two subsequent tests were negative. Her father died of tuberculosis, but she had not received antituberculous therapy. She was employed as a housekeeper and had a 20-pack-year history of cigarette consumption. She had not used alcohol for 16 years.

On physical examination she was deeply pigmented and icteric with normal vital signs. There was no palpable adenopathy. Her lungs were clear, and there was a soft systolic murmur over the left sternal border. Her liver was enlarged (17 cm) and nontender with a prominent left lobe. The spleen tip was palpable, and there was no digital clubbing.

Laboratory studies yielded the following values: serum sodium 126 mmol per liter, potassium 4.2 mmol per liter, hematocrit 0.25 (25%), mean corpuscular volume 66 fl, prothrombin time 9.6 seconds, leukocyte count 7.6×10^9 per liter, aspartate aminotransferase 2,484 μkatal per liter (normal 100 to 500), alanine aminotransferase 2,450 μkatal per liter (normal 100 to 750), alkaline phosphatase 4,466 IU per liter (normal 64 to 238), bilirubin 90.6 μmol per liter (normal 0 to 17.1), lactate dehydrogenase 2,801 μkatal per liter (normal 1,967 to 4,551), and cholesterol 23.6 mmol per liter (normal <5.2). The chest roentgenogram was normal except for a 1-cm left lower lobe nodule (Figure 1). Chest computed tomography confirmed the presence of this nodule (3 cm) and an additional 1-cm nodule in the left lower lobe (Figure 2). The mediastinal and hilar structures were normal. A needle biopsy of the liver disclosed chronic periportal fibrosis and inflammation, mild cirrhosis, and focal noncaseating granulomas. Acid-fast bacillus and fungal

TABLE 1.—*Disorders Associated With Primary Biliary Cirrhosis*

Pulmonary
Interstitial pneumonitis and fibrosis
Organizing pneumonitis
Bronchoalveolar lavage lymphocytosis with normal chest roentgenogram
Granulomas with or without sarcoidosis
Nonpulmonary
Sjögren's syndrome
Scleroderma
Rheumatoid arthritis
Psoriatic arthritis
Renal tubular acidosis
Autoimmune thyroiditis
Hypothyroidism
Avascular necrosis
Hypertrophic osteodystrophy
Chondrocalcinosis

stains were negative. A bone marrow biopsy revealed no stainable iron, and granulomas were not found. A sputum examination was negative for acid-fast bacilli. A fiberoptic bronchoscopy with transbronchial biopsy of the left lower lobe nodule revealed a noncaseating granuloma with a giant cell and a surrounding organizing pneumonitis (Figure 3).

Figure 1.—A posteroanterior chest roentgenogram shows an ill-defined left lower lobe nodule (arrow).

Figure 2.—A computed tomogram of the chest shows a left lower lobe nodule (arrow).

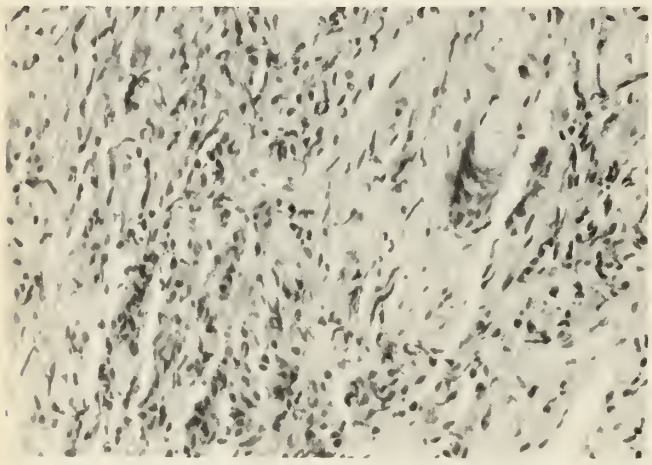

Figure 3.—A photomicrograph of a biopsy specimen of transbronchial lung shows a poorly formed granuloma containing a multinucleated giant cell (arrow). There is also a surrounding organizing pneumonitis (original magnification ×250).

Stains and cultures for fungal and acid-fast organisms were negative. She was discharged on corticosteroid therapy for a month. At this time the antimitochondrial antibody test returned positive at 1:256, confirming the diagnosis of primary biliary cirrhosis. Corticosteroids were discontinued. A chest roentgenogram two months after discharge revealed the disappearance of the pulmonary nodule, but liver test results remained abnormal.

Because of continued clinical deterioration and liver test abnormalities, she was evaluated for orthotopic liver transplantation. A new complaint was a nonproductive cough, but a chest roentgenogram was normal. The angiotensin-converting enzyme level was 27 IU per ml (normal 10 to 30), and a second test for antimitochondrial antibody was unchanged. Repeat chest computed tomography revealed new left superior and inferior hilar adenopathy and confirmed the disappearance of the lung nodules. Liver function continued to deteriorate, and her fatigue and pruritus worsened. She underwent orthotopic liver transplantation 11 months after her initial presentation.

The histologic examination of the native liver confirmed the diagnosis of primary biliary cirrhosis, revealing periportal granulomas, nonsuppurative invasion of the bile ducts, and cirrhosis. Postoperatively she has been maintained on a regimen of prednisone, azathioprine, and cyclosporine and has done well to date.

Discussion

Primary biliary cirrhosis has no clear cause. Although noncaseating granulomas can be seen, particularly in stage I disease, these almost always involve the liver parenchyma and occasionally the mesenteric and hepatic hilar lymph nodes. Extrahepatic manifestations are most often related to the developing liver failure. Hepatic osteodystrophy due to malabsorption and renal tubular acidosis have also been described.[8] Primary biliary cirrhosis infrequently occurs in association with Sjögren's syndrome, scleroderma, rheumatoid arthritis, psoriatic arthritis, chondrocalcinosis, hypertrophic osteodystrophy, and avascular necrosis.[9]

Pulmonary involvement in primary biliary cirrhosis is more controversial, and in large series pulmonary manifestations are uncommon.[8] Most often described in case reports are interstitial pneumonitis and fibrosis.[1,3] Weissman and Becker reported lymphocytic interstitial pneumonitis,[4] and Davison and Epstein described organizing pneumonitis and the CREST syndrome.[5] Wallaert and co-workers did bronchoalveolar lavage in 12 asymptomatic patients with primary biliary cirrhosis and normal chest roentgenograms. They found normal total cell counts but increased lymphocyte percentages.[6] Interestingly, expanded lymphocyte populations in bronchoalveolar lavage fluid have been described in patients with Crohn's disease and normal chest roentgenograms and are the hallmark of bronchoalveolar lavage findings in sarcoidosis.[10]

Extrahepatic granulomas have been recorded in patients with primary biliary cirrhosis. Fox and associates found hepatic granulomas in 29 patients with the disorder, and in 5 of the patients, granulomas also involved the hepatic, hilar, mesenteric, and mediastinal lymph nodes.[7] While intrapulmonary granulomas have been described in these patients, the possibility of coexistent sarcoidosis was raised.[11-16] In these reports, liver biopsies and serum antimitochondrial antibody tests confirmed the presence of primary biliary cirrhosis, and typical clinical and chest radiographic presentations of sarcoidosis were present as well. Stanley and Woodgate described two cases of confirmed

primary biliary cirrhosis and intrapulmonary granulomas.[2] In both patients, pulmonary symptoms, abnormalities on chest films, and antimitochondrial antibodies subsequently developed.[17] In one, the Kveim-Siltzbach skin test was negative. It is unclear if these cases represented pulmonary granulomas with primary biliary cirrhosis or coexistent sarcoidosis. Fox and colleagues described one case of primary biliary cirrhosis with intrapulmonary granulomas, but the results of a chest roentgenogram and pulmonary history were not mentioned.[7] Wallace and co-workers reported the case of a patient in whom nodular densities on a chest roentgenogram proved to be granulomatous. Follow-up studies were not available, but the possibility of sarcoidosis was not considered.[3]

The case reported here was initially diagnosed as primary biliary cirrhosis with pulmonary granulomas, a combination previously reported.[2,3,7,17] Sarcoidosis was not considered at first owing to the lack of symptoms and typical chest roentgenographic findings. Because of the disappearance of the pulmonary granulomas following corticosteroid treatment, progressive liver disease, and the appearance of hilar adenopathy when therapy was discontinued, this case is thought to represent the coexistence of primary biliary cirrhosis and sarcoidosis. To date there have been 12 such cases reported in the literature with varying degrees of documentation[3,11,12,14-17] as well as other cases of primary biliary cirrhosis or sarcoidosis with overlapping symptom complexes. While the incidence of pulmonary granulomas and alveolitis in this disease, whether due to a primary process or to sarcoidosis, is apparently small, the actual incidence may be underestimated because of the infrequent use of chest computed tomography in conjunction with bronchoalveolar lavage.

Although the differentiation of primary biliary cirrhosis from sarcoidosis may occasionally be difficult, the divergent natural history and therapeutic response make this distinction important. A patient with pruritus, jaundice, prominent liver disease, antimitochondrial antibodies, and greatly elevated alkaline phosphatase and cholesterol levels should suggest the disorder. Alternatively, a patient with prominent pulmonary symptoms, erythema nodosum, hypercalcemia, an elevated angiotensin-converting enzyme level, and abnormal chest roentgenogram and pulmonary function test results is more likely to have sarcoidosis. It could be speculated that the histologic similarities between primary biliary cirrhosis and sarcoidosis suggest a continuum of disease and possibly even a common pathogenesis.

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Editorials

Managing Congestive Heart Failure Medically—What Have We Learned?

In the past two decades there has been considerable progress in understanding the epidemiology, pathophysiology, and management of congestive heart failure. Elsewhere in this issue of the journal, Arai and Greenberg have masterfully reviewed the pertinent literature and provided a useful outline of the medical management of chronic congestive heart failure.[1] Congestive heart failure is a clinical syndrome that can result from a variety of causes: valvular heart disease, pericardial disease, hypertension, coronary artery disease, and myocardial disease. Myocardial dysfunction is the most common denominator, however, and, thus, determining the nature and severity of myocardial dysfunction is essential for the rational management of heart failure.

Diastolic Failure

It is well established that both systolic and diastolic ventricular dysfunction can precipitate congestive heart failure. The hemodynamic abnormalities and signs and symptoms of congestive heart failure are similar whether heart failure results primarily from diastolic or systolic dysfunction. For clinical purposes, diastolic failure is defined as "impaired capacity of ventricles to fill without an inappropriate rise of atrial pressures." If this definition is accepted, a number of clinical conditions can be recognized in which abnormalities of ventricular filling appear to be the principal mechanism of congestive heart failure (Table 1).

The mechanism of impaired ventricular filling in these different clinical conditions is different, and understanding the various pathophysiologic mechanisms of diastolic dysfunction is necessary for rational management. For example, when abnormalities of left ventricular filling result from mitral valve obstruction or acute aortic and mitral valve regurgitation, correcting these mechanical defects is the most appropriate treatment. Myocardial ischemia, ventricular hypertrophy, and systemic hypertension, even without hypertrophy, are more frequent causes of left ventricular diastolic dysfunction. The precise mechanism for altered diastolic function in these clinical conditions is not known. Fibrosis, hypertrophy, and cellular disarray, however, may increase left ventricular passive chamber stiffness and thus enhance diastolic resistance to left ventricular filling. Ischemia, asynchrony, abnormal calcium flux, abnormal ventricular loading, and hypertrophy may also be associated with abnormal myocardial relaxation and impairment of ventricular filling. The diagnosis of diastolic dysfunction is best accomplished by determining the various indices of ventricular filling and relaxation: left ventricular end-diastolic pressure, ventricular compliance, peak filling rate, time to peak filling rate, atrial filling rate, peak negative change in pressure with respect to the change in time, and the time constant for ventricular relaxation. For clinical purposes, the demonstration of a normal or near-normal ejection fraction by echocardiography or radionuclide ventriculography strongly suggests that diastolic dysfunction is the principal cause of congestive heart failure. As myocardial ischemia and hypertrophy are two common causes of diastolic dysfunction, it is desirable to investigate for their presence and severity.

The incidence of diastolic dysfunction as the principal cause of congestive heart failure is difficult to estimate. Arai and Greenberg point out that although some studies have suggested that the prevalence of "diastolic failure" may be as high as 36%, in their experience it is closer to 5% to 10%.[1] Obviously, the methods of assessing diastolic function will influence the estimation of the incidence of diastolic failure. If the various indices of ventricular filling and relaxation function as mentioned earlier are used, it is likely that some abnormalities of ventricular filling will be detected in many patients with congestive heart failure. On the other hand, if the presence of a normal left ventricular ejection fraction is used as the principal criterion for the diagnosis of diastolic failure, the prevalence is likely to be much lower.

Pharmacotherapy for diastolic failure is largely empirical. Diuretics and nitrates are helpful in relieving symptoms, but an exessive reduction of the left ventricular filling pressure may be associated with a reduction in cardiac output and hypotension. Digitalis and other inotropic drugs are ineffective and are relatively contraindicated. A number of pharmacologic agents have the potential to improve diastolic function. In some patients with hypertrophic cardiomyopathy, calcium entry blocking agents, particularly verapamil, improve left ventricular compliance and filling characteristics. The relief of ischemia with nitrates, β-adrenergic blocking agents, and calcium entry blocking agents may be associated with improved left ventricular filling, compliance, and relaxation. Angiotensin-converting enzyme (ACE) inhibitors also improve diastolic function not only in hypertensive patients but also in patients with heart failure resulting from ischemic and nonischemic dilated cardiomyopathy. Thus, it is reasonable to consider the use of these pharmacologic agents in appropriate subsets of patients, although their effectiveness in improving the prognosis of patients with diastolic failure is uncertain (Table 2).

Systolic Failure

As Arai and Greenberg point out, a number of therapeutic options, some old and some new, are now available in the treatment of congestive heart failure that results primarily from left ventricular systolic dysfunction. We know that diuretics are an effective and essential therapy for the relief of congestive symptoms. The reduction of systemic and pulmonary venous pressure is the predominant mechanism for these beneficial effects. We have also learned that long-term diuretic therapy does not increase cardiac output and, thus, symptoms related to low cardiac output are unlikely to be ameliorated with diuretic therapy alone. Furthermore, the long-term use of large doses of diuretics frequently induces renal failure and activates the renin-angiotensin-aldosterone system, which may increase left ventricular afterload

TABLE 1.—*Congestive Heart Failure Due to Diastolic Dysfunction*

Mitral valve obstruction
Constrictive pericarditis
Restrictive cardiomyopathy
Acute volume overload (aortic regurgitation, mitral regurgitation)
Myocardial ischemia
Ventricular hypertrophy
Hypertension

and produce adverse effects on cardiac performance. Thus, diuretic therapy alone cannot be recommended for the long-term management of heart failure.

Arai and Greenberg elegantly discuss the controversies regarding long-term digitalis therapy in the management of patients with heart failure in sinus rhythm.[1] The results of a number of prospective controlled studies indicate that long-term digitalis therapy is indeed effective in improving left ventricular ejection fraction, the clinical state, and exercise tolerance in the majority of patients with chronic heart failure, provided heart failure results from impaired systolic function.[2,3] It is uncertain, however, whether digitalis is effective in patients with depressed systolic function with no or minimal symptoms. Thus, at present long-term digitalis therapy can be recommended in almost all symptomatic patients with chronic heart failure with a reduced left ventricular ejection fraction, provided there is no overt contraindication (severe renal failure, digitalis toxicity).

Is diuretic and digitalis therapy sufficient for the effective management of chronic heart failure? A number of well-controlled prospective studies have now shown that the addition of direct-acting vasodilators—hydralazine hydrochloride and isosorbide dinitrate combination—or of ACE inhibitors to digitalis and diuretics not only improves the clinical state but also reduces mortality. In patients with mild to moderate heart failure, a 38% reduction in one-year mortality has been reported with the use of hydralazine-isosorbide dinitrate.[4] In patients with more severe heart failure (New York Heart Association class IV), ACE inhibitor therapy decreased the one-year mortality by 31%.[5] Thus, based on available information, the addition of hydralazine-isosorbide dinitrate or ACE inhibitors seems appropriate for the management of virtually all cases of symptomatic chronic heart failure. One practical question needs to be considered regarding vasodilator therapy for heart failure—whether hydralazine-isosorbide dinitrate or ACE inhibitors should be given preference. Angiotensin-converting enzyme inhibitors appear to provide some advantage over hydralazine-isosorbide dinitrate in that they decrease myocardial oxygen consumption more consistently. A favorable change in neuroendocrine abnormalities such as a reduction in catecholamines and angiotensin II and aldosterone levels occurs with the use of ACE inhibitors.[6,7] In addition, they have the potential to prevent ventricular remodeling and dilatation.[8] Thus, my own bias is to use ACE inhibitors in preference to hydralazine-isosorbide dinitrate, provided they are well tolerated and do not produce serious adverse effects.

Is there any other therapy for patients refractory or intolerant to vasodilators and ACE inhibitors? At present the alternatives are extremely limited, except for cardiac transplantation, which undoubtedly improves the prognosis in patients with end-stage heart failure. Intermittent intravenous inotropic therapy with dobutamine hydrochloride or phosphodiesterase inhibitors (amrinone, enoximone, milrinone) can improve the clinical state in some patients, but the duration of beneficial response is variable and the prognosis does not appear to be influenced by such therapy. A few, mainly uncontrolled studies have suggested that amiodarone and β-adrenergic blocking agents may be of benefit in patients with dilated cardiomyopathy.[9,10] Clinical experience with such therapy, however, is too limited to allow for an assessment of the effectiveness of these agents in the routine management of chronic heart failure. It is apparent that many investigations will be required to identify more appropriate and more effective pharmacotherapy for patients with refractory heart failure, without which the outlook will remain dismal. Nevertheless, based on available information, a rational therapeutic approach can be outlined for the management of systolic heart failure (Table 3).

TABLE 2.—*Outline of Monogement of Diastolic Failure*

Problem	*Therapy*
Congestive symptoms	Moderate dose of diuretics and nitrates
Diastolic dysfunction in hypertensive patients	Antihypertensive agents, particularly calcium entry blocking agents, ACE inhibitors, and certain β-blockers
Diastolic dysfunction resulting from ischemia	Nitrates, β-blockers, calcium entry blocking agents, revascularization
Diastolic dysfunction due to hypertrophy	Calcium entry blocking agents, ACE inhibitors
Diastolic dysfunction in hypertrophic cardiomyopathy	Calcium entry blocking agents, particularly verapamil

ACE = angiotensin-converting enzyme

TABLE 3.—*Outline of Monogement of Systolic Foilure*

Problem	*Therapy*
Minimal or no symptoms; postinfarction; left ventricular dysfunction	? ACE inhibitors
Mild to moderately severe heart failure	Digitalis, diuretics, and hydralazine-nitrates or ACE inhibitors
Severe heart failure	Digitalis, diuretics, and ACE inhibitors
Severe heart failure refractory to ACE inhibitors	Intermittent dobutamine or phosphodiesterase inhibitors, newer inotropic agents, amiodarone or β-blockers in selected patients; cardiac transplantation, if possible

ACE = angiotensin-converting enzyme

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Consider the Alternatives

CONSIDERABLE FUROR HAS ARISEN in the wake of the first report in the world "consistent with transmission of human immunodeficiency virus to a patient during an invasive dental procedure, although the possibility of another source of infection cannot be entirely excluded."[1] The report raises numerous issues such as the modes of transmission of human immunodeficiency virus (HIV), the reliability of retrospective epidemiologic investigations, and the usefulness of DNA sequencing in case analyses of this type. For physicians, part of the debate has centered on informed consent. That is, should patients be informed that their physician is HIV antibody-positive or has the acquired immunodeficiency syndrome (AIDS)? Scenarios have descended to the level of, "Let's make a deal. I'll tell you if you tell me." The issue is much broader than HIV and games.

The hepatitis B virus, for example, is far more prevalent than HIV and is also blood-borne. Hepatitis B virus clearly has been transmitted, very rarely, to patients in gynecologic and dental settings.[2,3] (Never forget that although hepatitis B is a disease preventable by recombinant vaccine, 200 to 300 health care workers, including physicians, die *every year* in the United States of hepatitis B contracted at work. If health care workers were successfully immunized, they would not die of hepatitis B nor transmit it.) Should patients be told their physician's hepatitis B status?

In addition to the possibility that infections might be transmitted by a physician (or dentist, laboratory technician, or nurse), the question of impairment must be addressed. A physician with AIDS may be too sick, too tired, or too demented to have the clarity, stamina, or judgment necessary to practice good medicine. A physician with hepatitis B may be in the same situation. Similarly, but aside from infectious diseases, a physician with a diagnosis such as cancer, cardiovascular disease, or manic-depressive disorder may be unable to "practice medicine with reasonable skill and safety to patients" (AMA Council on Mental Health, American Medical Association, 1972). A physician with an active addiction or in early recovery also may be impaired.

What should we tell our patients? Our colleagues? Our staff? Should physicians announce their HIV status or hepatitis B virus status or their potentially mind-damaging, life-threatening diagnoses or their chemical dependencies? Should they discuss their treatment status? Should consideration be given to physicians' privacy as well as patients' privacy?

The human immunodeficiency virus yet again has presented our profession with a challenge that goes far beyond the obvious. In this instance, the issue transcends disclosure of, or testing for, HIV infection. No one wants to die of AIDS nor transmit the virus. No one wants to die of hepatitis B nor transmit that virus. No one wants to damage patients or family because of impairment for any reason. We want to serve. What, if anything, should we tell our patients about our ability to do so? All or none? Case by case? Publicly or privately? What is best for patients? And physicians? And our profession? Our decisions must be based on science and prudence, compassion and reason. Thorough and unbiased education—of ourselves, our patients, and the public—will assure that we will deal effectively with misinformation, panic, prejudice, and fear. We must consider, and choose, the best alternatives.

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Correspondence

The Editors will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words and must be typewritten, double-spaced, and submitted in duplicate (the original typescript and one copy). Authors will be given the opportunity to review the editing of their correspondence before publication.

Decriminalizing Drug Use

To THE EDITOR: It is becoming increasingly clear that attempting to enforce a ban on certain illegal psychoactive substances through conventional law enforcement and court procedures is not possible without abrogating our long-standing individual protections under the Bill of Rights. Furthermore, it is exorbitantly wasteful and ineffective. It must also be recognized that alternative proposals dealing with the problem of harmful drug use have been few and lack specificity. In a recent debate on public television, proponents of legalization had no appropriate answers to Representative Charles Wrangel (Democrat, New York City), who wanted to know which drugs would be legally distributed, under what circumstances, and by whom.

I think that as a society we would be best served by pursuing a policy of selective decriminalization (not legalization) in an attempt to ameliorate the ravages of drug use. Laws pertaining to the sale or distribution of psychoactive substances would remain in effect. The *use* of psychoactive substances would no longer be a crime, but the user would be required to enter into a treatment program under medical management.

It is time to admit that we do not have a single solution to the problem of illegal drug use in our society. Selective decriminalization combined with medical intervention should be tried (even though treatment regimens are not proven effective) but only after a consensus is reached on how to best answer Representative Wrangel's excellent questions.

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The 'Aerospace Syndrome'

To THE EDITOR: I appreciate Dr Terr's editorial[1] in response to our article, "An Outbreak of Illness in Aerospace Workers,"[2] in the July issue and heartily concur with his analysis overall.

I am writing to clarify, as well as amplify with additional data, some of the points in the article. In the editorial Dr Terr commented that the "aerospace syndrome" apparently fit well into the category of illness previously described as "multiple chemical sensitivity."[1] In fact, only a subgroup (15) of the 53 workers described in our article actually met the previous definition of this syndrome.

This subgroup had a strikingly high prevalence of preexisting anxiety and depressive disorders, as described in a companion article.[3] Many of the other workers, who did not appear to meet the definition for "multiple chemical sensitivity," improved after being removed from exposure over the long term to phenol-formaldehyde composite materials. This suggests that psychological vulnerability may influence the chronicity of symptoms associated with the incident.

Not mentioned in detail in our article is the fact that the company made air measurements of phenol and formaldehyde in the workplace shortly after introducing the phenol-formaldehyde composite material. Levels were well below permissible exposure limits.

Low-level exposure to odors or respiratory tract irritants may stimulate the olfactory or trigeminal nerves, or both, and produce autonomic arousal,[1,4] perhaps through a mechanism involving the limbic system. The expression of illness is clearly multifactorial, and chemical exposure and odor alone probably are not sufficient to cause this and other similar outbreaks of illness. Nevertheless, given other psychosocial factors—which have yet to be clearly identified and measured—such low level irritant or olfactory stimulation may result in definite illness with features typical of acute anxiety and depression.[2] It is also possible that such symptoms may be due primarily to psychosocial factors and have little to do with chemical exposure at all.

The intense reluctance of patients, the public, and many health care practitioners to acknowledge the likely psychophysiologic nature of the illness in similar outbreaks of workplace illness attributed to environmental exposure may be because of the perception that psychological symptoms are somehow less "real" or legitimate expressions of illness. Also, the workers' compensation, legal, and administrative systems are less likely to accept or pay for treatment of psychological illness or injury, especially when the etiology is likely to be multifactorial and not attributable primarily to any direct "toxic" effect of individual or mixed chemical exposures.

The industrial hygienists who measure the air, the chemists who evaluate the chemical components of materials and processes, and the physicians who evaluate persons affected by similar outbreaks of illness are each looking at a piece of the elephant, and we have yet to clearly define the entire shape of the problem.

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Herpes Zoster Ophthalmicus—The Changing Epidemiology and Its Implications for Treatment

To THE EDITOR: Immunocompromised patients with herpes zoster ophthalmicus (HZO) are at risk for the development of disseminated disease as well as ocular complications.[1,2] Before 1983, we saw approximately six patients a year with HZO at the San Francisco General Hospital Medical Center (SFGH) Eye Clinic, a clinic with about 9,000 visits a year;

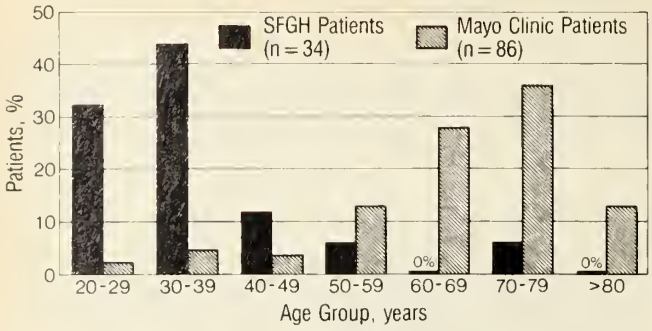

Figure 1.—The incidence of herpes zoster ophthalmicus by age in our series is compared with that of Womack and Liesegang's series.[2] SFGH = San Francisco General Hospital Medical Center

TABLE 1.—*Occurrence of Keratouveitis After Initiation of Acyclovir Therapy in Patients With HZO, n = 34*

	Patients, No.			
Route of Administration	*HIV-Positive*	*At Risk*	*HIV-Positive and At Risk*	*No Risk*
Oral	2/5	1/3	3/8	0/2
Intravenous	0/8	2/12	2/20	0/2
No therapy	...	...	...	0/2

HIV = human immunodeficiency virus, HZO = herpes zoster ophthalmicus

most of the HZO patients were elderly—older than 50 years.

More recently, along with the increase in the number of patients with the acquired immunodeficiency syndrome (AIDS) treated at SFGH, we have observed an increase in the number of HZO patients seen at our clinic: 36 patients with HZO were seen between January 1986 and May 1989. A review of the available medical records showed that 13 of 34 patients were known to be positive for the human immunodeficiency virus (HIV) at the time of presentation with HZO. Of the other 21 patients, 15 had risk factors for exposure to HIV, such as intravenous drug abuse, bisexuality, homosexuality, or prostitution, while 6 had no such risk factors.

The mean ages of the "known HIV-positive," "at risk," and "not at risk" groups were 36, 32, and 48 years, respectively. This differs from the previously reported age distribution for HZO, where most of the patients were older than 50 years (Figure 1).[2] The younger age distribution of the SFGH patients reflects the relative prevalence of zoster ophthalmicus in HIV-positive or at-risk persons in this population. The mean age of patients with HIV disease in San Francisco is 38 (Doug Franks, AIDS Surveillance Office, San Francisco Health Department, oral communication, March 30, 1990). This finding underscores the importance of considering HIV infection in young patients with HZO because it may be the initial manifestation of AIDS.[3-5] Moreover, Melbye and colleagues reported the cumulative incidence of AIDS to be 45.5% four years after an initial episode of HZO in a homosexual population.[3] Of our 15 at-risk patients, 9 of whom are homosexual, none has had a diagnosis of AIDS-related complex (ARC) or AIDS since the initial HZO episode. Our longest follow-up of these at-risk patients has been two years, however, and we may yet see the further sequelae of HIV disease in this group of patients.

In two of the HIV-positive patients, herpes zoster meningoencephalitis developed.[5] Such complications are anticipated in immunocompromised HIV-positive or at-risk patients. This has prompted us to treat aggressively all HIV-positive and at-risk HZO patients with intravenous acyclovir.

When the HIV-positive and at-risk groups were pooled, keratitis or uveitis developed in a larger percentage of patients on oral acyclovir treatment than on parenteral therapy (38% versus 10%, Table 1). Unfortunately, the small sample size limits the conclusions that can be drawn. In our potentially immunocompromised population, however, the administration of intravenous acyclovir does appear to reduce the occurrence of keratouveitis.

The younger age distribution of our HZO population suggests that in the future we will continue to see two predominant age groups of HZO—one a younger, HIV-associated group; the other, an elderly population. The therapeutic implications of this changing epidemiology are still unclear. We recommend treating all potentially immunocompromised patients with intravenous acyclovir (30 mg per kg per day for 5 days) followed by oral acyclovir (800 mg 5 times per day for 9 days) because this may prevent life-threatening dissemination as well as reduce the incidence of keratouveitis.

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Radon in California Homes

To the Editor: We would like to bring your readers up to date on issues raised in previous communications concerning radon in California homes.[1,2]

In March 1990 the California Department of Health Services (CDHS) published the results of a study of indoor radon concentrations in 310 California residences.[3] This survey was the first statewide effort to determine the extent of radon exposure in representative California homes and to identify areas of the state where residences may have elevated radon concentrations. In this study, radon measurements were carried out for a full year in order to obtain an accurate estimate of exposure unbiased by short-term fluctuations in radon levels because of weather conditions or changes in ventilation.

Confirming more limited earlier studies, the results of this most recently completed survey show that about 0.8% of California homes are expected to have annual average radon levels exceeding the current action level of 4 picocuries (pCi) per liter of air recommended by the United States Environmental Protection Agency (EPA). Of those homes having levels above 4 pCi per liter, none exceeded 20 pCi per liter.

The results also were analyzed by dividing the state into six geographic regions. The geometric mean radon concentration of the state was 0.85 pCi per liter. The geometric mean level in the Sierra Nevada region (from Placer County

south to Mariposa, as well as Alpine, Mono, and Inyo counties) was 2.20 pCi per liter, which was significantly higher than other areas. The Fresno-Ventura region (Madera, Fresno, Kings, Tulare, Kern, Santa Barbara, and Ventura counties) had the next highest level, with a geometric mean level of 1.31 pCi per liter.

Of the approximately 84,000 (confidence interval, 38,000 to 160,000) California homes predicted to have indoor radon concentrations above 4 pCi per liter, 54,000 (confidence interval, 24,000 to 97,000) are expected to be in the Sierra Nevada region (about 25% of 220,000 residences). This result is understandable in light of the extent of granitic rock formations (with higher uranium concentration than most rock types) and the harsher winters (with consequent "tighter" building construction, less ventilation, and larger pressure differences between home substructure and underlying soil due to the buoyancy of heated air) prevalent in this area.

The area with the next highest proportion of residences (3,000 to 16,000 of 1,000,000) expected to have radon concentrations above 4 pCi per liter is the Fresno-Ventura region. Portions of this region are currently undergoing intensive study by CDHS. In contrast, coastal counties north of Santa Barbara are projected to have less than 0.1% of homes (about 800 residences) above the EPA action level.

Data from this survey have been used by CDHS in designing more detailed surveys. For example, we are in the process of conducting a focused radon study of 800 homes in Ventura County and 200 homes in northwest Los Angeles County. In addition CDHS, in cooperation with EPA, is conducting a statewide survey of 3,000 homes whose selection was based on the analysis of the results in the six regions.

Overall, the accumulating data continue to show that California does not have a substantial problem with radon, although in selected areas of the state there is reason for some concern. Results of future surveys, combined with existing data, will allow us to make more precise recommendations regarding routine testing of homes for radon and the likelihood of the need for mitigation efforts.

In the meantime, while CDHS does not recommend, as a matter of public policy, that all California homes be tested for radon, we continue to encourage medical practitioners and the public to learn more about this environmental agent. Toward this end, we have produced a guidebook on radon,[4] as has the US Environmental Protection Agency,[5] which can be obtained by calling the CDHS Office of Radon Programs at (916) 324-2213. Information about radon contamination of water can be obtained by calling the department's Public Water Supply Branch at (415) 540-2172.

Persons who want their homes tested for radon can call the department's Office of Radon Programs at (916) 324-2213 to receive a list of companies that have demonstrated their laboratory proficiency in radon testing. Additional technical information also may be obtained by calling this number.

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5. A Citizen's Guide to Radon, What It Is and What to Do About It. Washington, DC, Environmental Protection Agency, 1986

Lessons From the Practice

Just a Day on the Beach

ARTHUR G. MADORSKY, MD, *Claremont, California*

Cessna 738 Tango November slants smoothly onto the base leg—ahead are the sandstone cliffs, to the left at 45 degrees off my shoulder are the white sand beach, the ocean, and the straggling, irregular line of our patients.

An easy turn to final, 40 degrees of flaps, and the rumble of the gear on the sand, followed by a short roll with easy throttle to save the propeller, then the familiar shudder and silence.

Carrying our bagged equipment and medicine, we move quickly to triage. "Eyes over there, Doc . . . hearts and lungs near the generator, Doc, so you can power the EKG"; "Doc, legs and arms and backs go near the plane so they can lean against it during exams and casting."

The morning's surgical procedures go well—12 more cataracts extracted, the patients to be seen next month. Twelve with cataract extractions from last month are fitted with old spectacles contributed by the folks back home—with the wondering smiles of newfound sight.

Juan's congestive heart failure is better; he has climbed down from the mountain 12 miles away to let us know—"Oh, yes, here's the fresh trout Mamasita prepared for you."

The young woman with polio isn't doing well this month—more weakness and pain—but she has managed to crutch her way 18 miles to the beach. She smiles because she wants us to have the carved crucifix her son has made. "No matter that you are Jewish—it's all the same God." She's right, of course.

Evening, and the fire lights the cold aluminum bird. I move to protect its windscreen from salt spray and savor the quiet chatter of family and newfound friends. I pop the top of the plane's engine to check the oil. Everyone looks up at the metallic sound, suddenly aware that tomorrow we will wing our way back to "our daily bread," leaving behind something of ourselves here on the beach but taking with us that special feeling that happens each time, the quiet feeling that transcends and makes speech a bother.

Morning, and 10 degrees of flaps, off the beach at 52 knots, and the teased stall horn whimpers. A brief look at the empty beach where magic and medicine and a small blue and white airplane came together briefly and made healing and love. And then home.

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
STEPHEN J. McPHEE, MD
Series' Editors

(Madorsky AG: Just a day on the beach. West J Med 1990 Oct; 153:448)

Dr Madorsky is in private practice in Claremont, California.
Reprint requests to Arthur G. Madorsky, MD, 1738 Bridgeport Ave, Claremont, CA 91711.

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See adjacent page for Brief Summary of Product Information

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BRIEF SUMMARY

The following is a brief summary only. Before prescribing, see complete prescribing information in Zantac® product labeling.

INDICATIONS AND USAGE: Zantac® is indicated in:
1. Short-term treatment of **active duodenal ulcer.** Most patients heal within four weeks.
2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathological hypersecretory conditions** (eg, Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of **active, benign gastric ulcer.** Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated.
5. Treatment of **gastroesophageal reflux disease (GERD).** Symptomatic relief commonly occurs within one or two weeks after starting therapy. Therapy for longer than six weeks has not been studied.

In active duodenal ulcer; active, benign gastric ulcer; hypersecretory states; and GERD, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: Zantac® is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS:

General: 1. Symptomatic response to Zantac® therapy does not preclude the presence of gastric malignancy.
2. Since Zantac is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since Zantac is metabolized in the liver.

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during Zantac therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although Zantac has been reported to bind weakly to cytochrome P-450 *in vitro*, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions that suggest that Zantac may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2,000 mg/kg/d.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, Escherichia coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Zantac. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Zantac is secreted in human milk. Caution should be exercised when Zantac is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with Zantac®. The relationship to Zantac therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to Zantac administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported.

Cardiovascular: As with other H_2-blockers, rare reports of arrhythmias such as tachycardia, bradycardia, atrioventricular block, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, abdominal discomfort/pain, and rare reports of pancreatitis.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid intravenously for seven days, and in 4 of 24 subjects receiving 50 mg qid intravenously for five days. There have been occasional reports of hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice. In such circumstances, ranitidine should be immediately discontinued. These events are usually reversible, but in exceedingly rare circumstances death has occurred.

Zantac® 150 and 300 (ranitidine hydrochloride) Tablets
Zantac® (ranitidine hydrochloride) Syrup

Musculoskeletal: Rare reports of arthralgias.

Hematologic: Blood count changes (leukopenia, granulocytopenia, thrombocytopenia) have occurred in a few patients. These were usually reversible. Rare cases of agranulocytosis, pancytopenia, sometimes with marrow hypoplasia, and aplastic anemia have been reported.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by Zantac and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when Zantac has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving Zantac, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia), anaphylaxis, angioneurotic edema, and small increases in serum creatinine.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: (See complete prescribing information in Zantac® product labeling).

Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice daily. An alternate dosage of 300 mg or 20 ml (4 teaspoonfuls equivalent to 300 mg of ranitidine) once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.

Maintenance Therapy: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day. In some patients it may be necessary to administer Zantac® 150-mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/d have been employed in patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day.

GERD: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day.

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with Zantac, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: Zantac® 300 Tablets (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 (NDC 0173-0393-40) tablets and unit dose packs of 100 (NDC 0173-0393-47) tablets.

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Store between 15° and 30° C (59° and 86° F) in a dry place. Protect from light. Replace cap securely after each opening.

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July 1990

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- Join the largest department within this multispecialty group (15 Family Practitioners)
- Immediate in-house specialty consultation
- Well trained administrative support to assist in business matters, while allowing autonomy regarding the decisions of your practice
- Attractive benefit package includes excellent salary leading to early shareholder status

SPOKANE, WASHINGTON (metropolitan population 350,000) offers very affordable housing, unlimited year-round recreation, excellent schools, and numerous cultural organizations.

CONTACT:
Colleen Mooney
Recruitment Coordinator
Rockwood Clinic
E. 400 Fifth Ave
Spokane, WA 99202
(509) 838-2531

LOS ANGELES. Small multispecialty group seeks second Pediatrician and OB/GYN to work with present physicians. Excellent compensation and benefits. Looking for long term partners. Call or send CV to Craig Kaner, All Care Medical Group, 2675 E. Slauson Ave, Huntington Park, CA 90255; (213) 589-6681.

INTERNIST—PACIFIC NORTHWEST. Excellent opportunity for BC/BE Internist to join group of five Internists in suburban Idaho community. Near urban referral center with good subspecialty backup. Also near superb hunting, fishing, camping, and skiing. Please call or refer résumé to Susan Davis, Administrator, Caldwell Internal Medicine Professional Association, 222 E. Elm, Caldwell, ID 83605; 1 (208) 459-4667.

CALIFORNIA, MONTEREY BAY. Full-/part-time positions available with Monterey Bay's largest and most successful Urgent Care network. Generous guarantee, incentive plan, and benefit package. Malpractice covered. Practice in California's most beautiful coastal recreational area. BC/BE Emergency Room Medicine or Family Practice specialists preferred. Contact Bob Morris, MD, FACEP, Doctors on Duty Medical Clinics, 223 Mt Hermon Rd, Scotts Valley, CA 95066; (408) 438-9341.

ONCOLOGY. Seattle, Washington suburb. Join established Oncologists in private practice. For details, call Eloise Gusman, 1 (800) 535-7698 or send CV to PO Box 1685, Covington, LA 70434-1685.

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Good People Good Medicine

NORTHERN CALIFORNIA

Several positions available for Family Practice, Internal Medicine, and most medical subspecialties. We are a young, aggressive group in a well known prepaid group practice HMO organization with excellent benefits and a very reasonable call schedule. You will have a rewarding practice opportunity with ample time to enjoy the mountains and San Francisco which are nearby. If interested please call or send CV to Physician Recruitment, Administration, The Permanente Medical Group, Inc, 1305 Tommydon St, Stockton, CA 95210; (209) 476-3300.

CENTRAL OREGON. Family Practitioner sought for 7 member Family Practice group in heart of Oregon's best outdoor recreation. BE/BC Family Practitioner with experience in OB preferred. Excellent opportunity close to Cascade Mountains—skiing, hiking, fishing. Contact Jean Erickson, Prosearch, 305 NE 102nd Ave, Portland, OR 97220; (800) 622-3377.

FAMILY PRACTICE RESIDENCY DIRECTOR and full-time faculty position for BC Family Physician in an 18 resident, eight faculty program affiliated with University of California, Davis. Large clinical component with inpatient, outpatient, and routine OB skills needed. Send inquiries to T. N. Ernst, MD, PO Box 231, Merced, CA 95340-0231; (209) 385-7172.

EMMETT, IDAHO, rural community of 5,000 (12,000 in county) located 25 miles from Boise, is seeking residency trained Family Practitioner to enter full-time practice. First year salary guarantee $60,000 with incentive. Located close to several downhill ski areas as well as many other recreation opportunities such as hunting, fishing, camping. Inquires: please call Newton States, Hospital Administrator; (collect) (208) 365-3561.

MONTEREY PENINSULA, CALIFORNIA. BC/BE Primary Care Internist to join multispecialty group in ocean front resort community. Adjacent to Pebble Beach, Carmel. Guaranteed income leading to partnership in eight to twelve months. Busy, well established practice. Excellent office, lab, and x-ray departments. Outstanding community hospital. Submit CV, availability date to John D. Lord, MD, Central Medical Group, 505 Central Ave, Pacific Grove, CA 93950.

SAN FRANCISCO/EAST BAY. Experienced Primary Care Physicians needed at an Emergency Service fast track. This may be a part-time position; our need is for 32 hours per week in eight hour shifts on Saturdays and Sundays only. Physicians may work from one to four weekends a month. Remuneration is hourly and is highly competitive for the bay area. PO Box 5138, Berkeley, CA 94705.

SACRAMENTO—BE/BC General Internists. Successful stable multispecialty group. Opportunity to practice full range of inpatient and outpatient Internal Medicine. Full access to diagnostic, therapeutic, and consultative services. Academic affiliation with University of California, Davis, teaching residents in our hospital. In house CME. We are Kaiser Permanente—a physician managed, well established steadily growing group. Outstanding starting salary and advancement, benefit package, and retirement. Sacramento is California's boom town. Excellent schools. Family life-style. This is a quality career opportunity. Please call or send CV to Dennis Ostrem, MD, The Permanente Medical Group, Inc, 2025 Morse Ave, Sacramento, CA 95825; (916) 973-5781. EOE.

ALL SPECIALTIES/DESIRABLE PRACTICE OPPORTUNITIES AVAILABLE CALIFORNIA AND NATIONWIDE

Let us find you the practice that meets your specifications and geographical preference. There is no fee to the physician for our professional service. All inquiries are held in strict confidence. BC/BE physicians send CV or call:

Sharon Mac Kenzie
Mac Kenzie & Associates
PO Box 1240
Trinidad, CA 95570
1 (800) 735-4431
FAX: (707) 677-3033

STAFF PHYSICIAN. Join us in providing comprehensive medical care for 330 developmentally disabled children and adults at the Wyoming State Training school. Three physicians and one physician's assistant staff our 18-bed health care center and provide medical support to nursing, therapists, professional and paraprofessional staff across campus. Good working relationships with excellent hospital and medical group in local community. Progressive habilitation-oriented working environment. Attractive benefits, malpractice insurance provided, no overhead. Annual salary range $50,000 to $70,000 depending upon experience and qualifications. Campus situated in pleasant west-central Wyoming community of Lander, minutes from beautiful Wind River Mountain Range and close to Yellowstone and Grand Teton National Parks. Outstanding hiking, fishing, hunting, skiing, wilderness areas nearby. Good schools and services, low cost of living, no state income tax. Contact Director of Clinical Services, Wyoming State Training School, 8204 State Highway 789, Lander, WY 82520; or call (307) 332-5302. Equal Opportunity Employer.

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CLASSIFIED ADVERTISING INFORMATION

(415) 882-3376

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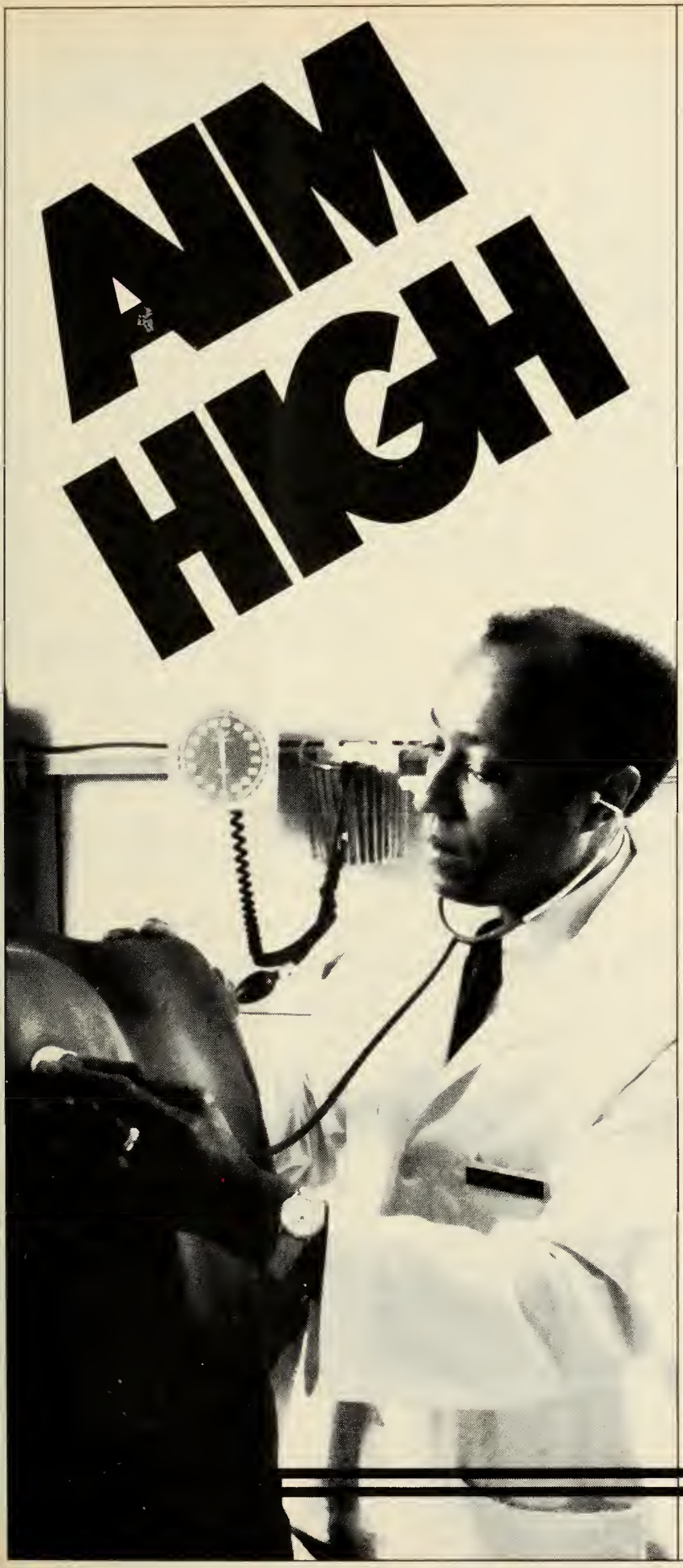

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Pleasant surroundings conducive to outdoor recreation. Excellent way to unwind from a life of strenuous private practice with rising insurance costs. Staff physician to provide medical care to ICF and psychiatric patients. Research possibilities; 40-hour week flex-time and weekend call. Local university for continuing education. Excellent fringe benefits.

Contact medical director at (505) 454-2422 or

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Box 1388
Las Vegas, NM 87701

(Continued from Page 452)

PHYSICIANS WANTED

SOLO WOMAN OB/GYN in busy practice in north Orange County, California, seeks BC/BE associate. Excellent patient base, streamlined efficient office, suburban life-style in fast growing community. Salary is competitive with good benefits and excellent partnership opportunity. Send résumé to Mary Monaghan, RN, Office Manager, 1275 N. Rose Dr, Ste 124, Placentia, CA 92670.

UNIVERSITY OF CALIFORNIA, DAVIS MEDICAL CENTER. The University of California, Davis, Department of Emergency Medicine is searching for physicians residency trained or BC in Emergency Medicine. The Health Science Campus is located in Sacramento and serves a large area of northern California. The Emergency Department cares for over 60,000 patients a year. The Center operates as a Level One Trauma Center, has paramedic base station training responsibilities, and has a helicopter service. An approved Emergency Medicine Residency Program began in July 1990. Emergency Physicians supervise medical students, interns, and residents, in addition to having direct patient responsibilities. Support for clinical research is available to those interested. University compensation is competitive, and fringe benefits include health and dental insurance, three weeks paid vacation, one week continuing medical education, social security, UC retirement plan, 12 paid holidays per year, and full malpractice coverage. Send CV to Robert W. Derlet, MD, Chief, Division of Emergency Medicine, University of California, Davis, Medical Center, 2315 Stockton Blvd, Sacramento, CA 95817.

ALASKA—A 10 physician multispecialty group in Anchorage is now seeking to add their second Neurologist. For more information send CV to Gordon Crawford, Manager, Professional Relations, Dept HH-10A, 500 W. Main St, Louisville, KY 40201-1438, or call toll-free 1 (800) 626-1590.

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Needed: Two Internists Two Family Practitioners WYOMING

PROFESSIONAL BENEFITS: private practice or join an existing practice; market area 100,000; 20% Medicare; a stable economy supported by major oil and coal companies; regional opportunities; the hospital features excellent clinical facilities, advanced equipment and technology; 85% of the medical staff is Board Certified.

MOVING YOUR PRACTICE: rent subsidies; salary/income guarantees, relocation expenses, practice marketing assistance.

PERSONAL BENEFITS: great place to raise a family; abundant clean air and recreation; community emphasizes quality family life; low crime rate; located between the Black Hills of South Dakota and Big Horn Mountains of Wyoming.

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Campbell County Memorial Hospital
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(Continued on Page 455)

(Continued from Page 454)

PHYSICIANS WANTED

PHYSICIANS

PRIMARY CARE

CALIFORNIA

JSA, Inc. is currently offering physicians full, part-time, and PRN positions in Primary Care Clinics located in San Diego and Sacramento.

BENEFITS PACKAGE

- **Flexible day-time hours**
- **No "on-call" requirement**
- **Malpractice insurance reimbursement**
- **Professional development funding**
- **Incentive programs**
- **Exceptional salary level**

QUALIFICATIONS

- **BC or graduate of an approved residency program in a Primary Care Specialty**
- **MD or DO**
- **Current state licensure**
- **ACLS/BCLS**

A proposed project in Oceanside includes positions in Emergency Medicine and Primary Care Specialties.

For further information, please contact Susan Bray, Recruiting Director at (301) 964-2811. JSA, Inc., PO Box 1305, Columbia, MD 21044.

JSA

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Consulting - Management - Services

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PHYSICIANS WANTED

SEATTLE: BC/BE General Internist to practice on Mercer Island, join BC Internists' group with three Seattle area offices. No income guarantee; group and location excellent. Write Dr Paxson, 3236 78th Ave SE, Ste 104, Mercer Island, WA 98040.

RADIOLOGIST—SAN FRANCISCO BAY AREA. Growing outpatient imaging practice with CT/MRI. Salary leading to partnership. Send CV to Murray Solomon, MD, 450 Sutter St, Ste 835, San Francisco, CA 94108; (415) 296-8654.

PEDIATRICIAN BC/BE for hospital-based teaching practice. Interest and training in Neonatology and Critical Care Pediatrics preferred. Join three full-time Pediatricians, two full-time Neonatologists, and one full-time Pediatric Surgeon in hospital with Community Level NICN and busy inpatient and outpatient services. Paid malpractice. Salary negotiable based on training and experience. Submit CV and references to Patricia A. Dixon, MD, Director, Pediatrics/Neonatal Services, San Joaquin General Hospital, PO Box 1020, Stockton, CA 95201; (209) 468-6600. AA/EOE.

LAKE ARROWHEAD, CALIFORNIA. Immediate openings for Emergency Physicians to staff low volume emergency department in wonderful location. Directorship also available. Guaranteed $115,000 per year. Directorship $130,000 per year; paid malpractice. Contact Richard Gillespie, MD, Quantum Emergency Medical Associates, PO Box 2467, Santa Rosa, CA 95405; (707) 546-4199.

OB/GYN, PEDIATRICS. Nevada and Washington. Private practices available with established OB/GYN physicians in Seattle suburb, Las Vegas and Sparks/Reno. Hospital sponsored Pediatric practices available in the above locations. For details, call Eloise Gusman, 1 (800) 535-7698 or send CV to PO Box 1685, Covington, LA 70434-1685.

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NORTHERN CALIFORNIA

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STABILITY

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The Permanente Medical Group, the largest multispecialty group practice in the U.S., is undergoing explosive growth in its Northern California region: the San Francisco Bay Area, Sacramento and the Central Valley. Our rapid increase in membership has created practice opportunities throughout the region.

Our physician-managed group is part of the comprehensive Kaiser Permanente Medical Care Program. As a TPMG physician, you have access to the latest medical technology and resources, the support of colleagues in all subspecialties — and the opportunity to provide excellent health care without the burdens of managing a practice.

TPMG offers many benefits: scheduled time off with cross-coverage provided by your colleagues, continuing education, malpractice insurance, a substantial retirement program and special arrangements for physicians transferring from established practice. For complete information, call or send CV to: The Permanente Medical Group, Inc., Richmond Prescott, M.D., Physician Recruitment Services, Dept. WJM-7153, 1814 Franklin, 4th Floor, Oakland, CA 94612. (800) 777-4912. EOE

KAISER PERMANENTE

Good People. Good Medicine.

(Continued on Page 456)

(Continued from Page 455)

ORTHOPEDIC SURGEON

BC Orthopedic Surgeon needed for office practice in beautiful southern California area. Full- or part-time, surgery optional. Excellent compensation package. Send CV to **Ronald Gilbert, MD, c/o Gilbert Medical Group, 1076 E. First St, #A, Tustin, CA 92680; or call (714) 832-1516.**

CENTRAL CALIFORNIA MULTISPECIALTY. Internist, Cardiologist, Dermatologist, Pediatrician, Orthopaedic Surgeon. 43 physician multispecialty group in beautiful city of 75,000, 45 minutes from Sierras, three hours from Los Angeles and San Francisco. Fee-for-service practice. Salary guarantee plus incentive, all corporate fringes. BC/BE only. Contact Gerald Moore, Administrator, Visalia Medical Clinic, Inc, 5400 W. Hillsdale Dr, Visalia, CA 93291; (209) 733-5222.

INTERNIST/FAMILY PRACTITIONER. For Geriatric health center. San Francisco bay area. Provide 24 plus hours per week in clinic, share on-call and hospital coverage. $33-35 per hour. California MD license. Call (415) 644-6060.

UROLOGIST. BC/BE, for northern California/San Francisco bay area, county hospital with Family Practice residency and university affiliation. Call Mr Frank Puglisi, CEO, at (415) 370-5100 or Dr Michael Baker, Chief of Surgery, at (415) 646-1360.

ARIZONA. Thomas-Davis Medical Centers, PC, a rapidly expanding multispecialty group practice of 110 plus physicians in Tucson, Green Valley, and Phoenix, Arizona has positions available in these cities in Family Practice, Internal Medicine, and Pediatrics. Excellent fringe benefits and profit sharing program. Guarantee for first two years, plus incentive. Early shareholder. Fee-for-service, as well as physician owned HMO. Must be BC/BE. Call or write Bill De Long (602) 322-2525 or James J. Vitali, CEO, (602) 322-2525 at Thomas-Davis Medical Centers, PC, PO Box 12650, Tucson, AZ 85732.

SACRAMENTO, URGENT CARE. $120,000 guaranteed at free standing, hospital affiliated clinic with an annual census of 18,000. Prestigious northern California group seeks qualified, experienced physicians, BC or BP in specialty. Additional opportunities at two area hospitals' ED Fast Tracks. Paid malpractice and generous profit sharing. Contact Art Wong, MD, FACEP, Emergency Physicians' Medical Group, 120 Montgomery, Ste 1000, San Francisco, CA 94104; (415) 989-1242.

OPPORTUNITY FOR GENERAL SURGEON with Thoracic and Vascular experience. Salary leading to partnership. Northern California surgical group in northern California rural community. Excellent quality of life. 1165 S. Dora, A3, Ukiah, CA 95482; (707) 462-7579.

THE VA MEDICAL CENTER AT PRESCOTT, ARIZONA, is recruiting for physician (Internist/Family Practice) in an Ambulatory Care setting. The Medical Center is a 200-bed general medical and surgical facility with a staff of approximately 650 employees. It is situated on the grounds of historic Fort Whipple. Prescott is a community of 25,000 set in the ponderosa pine foothills of the Bradshaw range of the Rocky Mountains. At an elevation of 5,400 feet, the benefits of four seasons are enjoyed. Outdoor recreation and sports abound—year-round tennis and golf, 100 miles to alpine skiing, fishing, sailing, boating on beautiful Lake Mead and Lake Powell. Two hundred miles to the excitement and night life of Las Vegas. All this in a quiet tree-lined community with 54 churches, a full service regional medical center, three colleges, six libraries, an excellent school system, a negligible crime rate, no pollution, low taxes, and reasonable housing prices. If you are interested in joining us in this idyllic life style and possess the requisite skill and an absolutely spotless professional or employment history, then contact Sharon K. Harmeson, at (602) 445-4860 ext 254, VAMC, Prescott, AZ 86301. An Equal Opportunity Employer.

EMERGENCY MEDICINE OPPORTUNITIES 107K-180K

CES of St. Louis, Inc, is currently seeking physicians interested in Emergency Medicine opportunities in the Central/Midwest area.

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If you are interested in looking into these opportunities, call our toll-free number for further details.

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OB/GYN, INTERNISTS, Family Practitioners, Pediatricians for Arizona and western opportunities. Quality positions available other regions of country. Inquiries confidential. Mitchell & Associates, PO Box 1804, Scottsdale, AZ 85252; (602) 990-8080.

CALIFORNIA—NORTHERN. Area's leading private practice group has immediate and future positions for BC/BE Family Practice and Primary Care Physicians in its Department of Ambulatory Care and General Medicine. Excellent compensation, incentive program, full benefits, early equity position, retirement plan. Experience life-style and professional fulfillment in beautiful northern California. Call Maureen Forrester: (408) 282-7833. Send CV to San Jose Medical Group, Inc, 45 S. 17th St, San Jose, CA 95112.

DENVER. Primary Care Physician for ger/adults and one BE/BC Psychiatrist $74,294 plus benefits, faculty appointment. Contact B. J. Brooks, MD, Assoc Director, FLMHC, 3520 W. Oxford Ave, Denver, CO 80236; (303) 762-4117. AA/EOE.

SACRAMENTO AREA. Immediate opening for BC/BE Family Practice Physician to join busy seven member group. Guaranteed salary and excellent benefit package. Partnership offered after two years. Opportunity to practice full range of primary medicine including Pediatrics, Geriatrics, and inpatient care. Excellent community to practice medicine with affordable housing, excellent schools, and state of the art hospital facilities. Send CV to Craig Lyon, 1219 30th St, Sacramento, CA 95816; (916) 737-0226.

SAN FRANCISCO BAY AREA—Occupational Health/Ambulatory Care center, Monday through Friday days; no nights, weekends or holidays required. Seeking Family Practice or Emergency Medicine experienced physician with keen interest in Occupational Medicine. Salary $100K plus. Send CV to Chase Dennis Group, 400 Taylor Blvd, #330, Pleasant Hill, CA 94523; (415) 676-2555.

PATHOLOGY DIRECTOR/SOUTHERN CALIFORNIA. BC, California licensed, clinically/anatomically trained with three to five years community hospital director experience needed to run Pathology department in 230-bed community hospital. Beautiful beach location in moderate sized city with excellent outdoor activity opportunities. Send CV to Administration, Community Memorial Hospital, Loma Vista at Brent, Ventura, CA 93003; or call (805) 652-5005.

SAN FRANCISCO BAY AREA. Private practice group seeking an associate in Internal Medicine. Other specialties needed for placement in northern and southern California, Oregon. For information call Bradshaw Associates, 21 Altamount, Orinda, CA 94563; (415) 376-0762, FAX (415) 376-0813.

PSYCHIATRIST, director, needed for two California CMHC. $100K per year, paid malpractice. Older MDs are encouraged to apply. Résumé to Number 215, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

CARDIOLOGIST. BE/BC to join busy two person Cardiology group on the Los Angeles west side. Excellent opportunity for the active practice of clinical, consultative, invasive, and noninvasive Cardiology plus UCLA teaching affiliation. David Cirauld, MD, 323 N. Prairie, Inglewood, CA 90301.

BEAUTIFUL MONTEREY BAY. Immediate opportunity for a friendly, skilled, Family Practice or Emergency Physician to join highly respected Urgent Care group with two beautiful Santa Cruz clinics. Committed to high quality care. Nice people, flexible scheduling, comprehensive benefits, including paid malpractice, group health insurance, long-term disability insurance, no nights, rapid advancement to full partnership in an outstanding place to live. Please send CV to Stanley Hajduk, MD, 6800 Soquel Dr, Aptos, CA 95003; or call (408) 662-3611.

FAMILY PRACTICE—SACRAMENTO. Kaiser Permanente is seeking BC/BE Family Practice Physicians to join the Division of Family Practice. We offer a challenging position that provides both outpatient and inpatient experience and enjoys close support from the specialty departments. We offer our patients high quality medicine and our physicians a practice with a high degree of professional and personal satisfactions. You will be joining a unique organization with a long, successful track-record and will benefit from the financial security associated with its success. Sacramento is a large diverse city providing a relative low cost of housing and is rich in cultural activities. It is also 90 miles from San Francisco and Lake Tahoe recreation areas. For additional information contact Stuart Hahn, MD, The Permanente Medical Group, Inc, 3240 Arden Way, Sacramento, CA 95825; or call (916) 973-5546. EOE.

OPPORTUNITY for full- and part-time Emergency Physicians. Excellent fee-per-patient load ratio. Malpractice paid. Also, Emergency Department/Family Practice positions for urgent care/industrial center. Send CV to Front Line Community Physicians, PO Box 10610, Santa Ana, CA 92711, or contact Medical Director at (714) 771-3290.

SOUTHERN CALIFORNIA—SPINE SURGEON. An Orthopedic Surgeon with training in Spine Surgery is needed to join two busy, well established Orthopedic Surgeons in Los Angeles County. Unlimited potential since this expertise is not represented in the group's service area. For more information about this opportunity, call toll-free 1 (800) 626-1590, or send your CV to Gordon Crawford, Professional Relations, Humana Inc, Dept HH-10C, 500 W. Main St, Louisville, KY 40201-1438.

MARYSVILLE (YUBA CITY). Primary care provider. Northern California primary care clinic with large Medi-Cal clientele. Three physicians, two physician assistants. No OB. No surgery. Near mountains, close to Sacramento, 2½ hours to Lake Tahoe and San Francisco. Salary $86,113 plus. Please contact Ed Allen, 938 14th St, Marysville, CA 95901; or call (916) 741-6244.

(Continued on Page 457)

(Continued from Page 456)

PHYSICIANS WANTED

FAMILY PRACTITIONER
GENERAL INTERNIST
OTOLARYNGOLOGIST
PEDIATRICIAN

Multispecialty group located in San Luis Obispo, California, seeks BC/BE physicians. Fringe benefits plus practice costs paid and shareholder status. Submit your CV to:

Physician Recruitment
San Luis Medical Clinic
1235 Osos St
San Luis Obispo, CA 93401

INTERNISTS. Nevada, California, Texas, Louisiana, Florida! Private practices available to join established physicians or to buy established practices. For details, call Eloise Gusman, 1 (800) 535-7698 or send CV to PO Box 1685, Covington, LA 70434-1685.

ALASKA—The only Vitro-Retinal specialist in Anchorage is now seeking an associate with similar skills. For more information send CV to Gordon Crawford, Manager, Professional Relations, Humana Inc, Dept HH-10B, 500 W. Main St, Louisville, KY 40201-1438, or call toll-free 1 (800) 626-1590.

RADIOLOGIST FOR SOUTHEASTERN UTAH. Excellent practice opportunity to join second Radiologist. Primary service area of 30,000 people with 88-bed community hospital. Nuclear, CT, mammography, ultrasound, and radiography. Contact Milton Bauermeister, MD, Castleview Hospital, Price, UT 84501; (801) 637-4800, ext 280 or (801) 472-5403.

EUGENE, OREGON. FAMILY PRACTICE. 36 physician multispecialty group is seeking BC/BE Family Physician. OB optional. Excellent schools. Abundant cultural and recreational opportunities. Near Cascade Mountains and coast. Home of University of Oregon. Please send CV to Rob Daugherty, MD, Oregon Medical Group, 2484 River Rd, Eugene, OR 97404; or phone (503) 688-9140.

SEEKING A PHYSICIAN to associate with a Family Practice group. Ultramodern facility with outpatient surgical suite and industrial medical center. Located in Corona, California, between Orange County and San Diego. Growing area. Good climate. We are offering an association with excellent economic advantage. Contact Ann Holmes at (714) 734-2042.

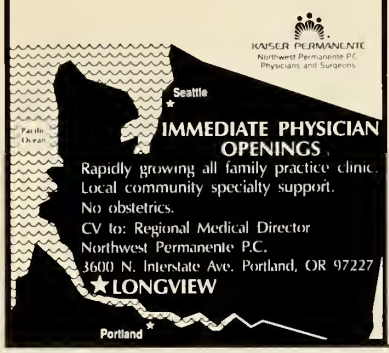
ARIZONA. VA Medical Center, Prescott, Arizona. Imaging Service is accepting applications for a full-time Radiologist. Competence and proficiency in interpreting CT scans is required. Prescott is a 217-bed General Medicine hospital with a busy combined Radiology and Nuclear Medicine service. Prescott is located in the mountains of north central Arizona with a population of 25,000. Commitment and selection is dependent upon obtaining and installing a CT scanner. Salary, approximately $80,000, dependent on qualifications. Send CV to Mary M. Poncel, MD, Chief of Imaging Service, VA Medical Center, Prescott, AZ 86313; or call (602) 445-4860, ext 214. An Equal Opportunity Employer.

ACADEMIC INTERNIST. Full-time faculty position for BC Internist at county hospital-based training program in northern California's central valley. Responsibilities include strong emphasis on teaching, administration, and research activities. Send CV or contact Sheela Kapre, MD, San Joaquin General Hospital, PO Box 1020, Stockton, CA 95201; (209) 468-6618. Affirmative Action/Equal Opportunity Employer.

MENDOCINO COUNTY. Immediate opening in beautiful coastal northern California for full-time BC/BE General/Vascular Surgeon with trauma experience. Send CV to Julie Campbell, Mendocino Coast District Hospital, 700 River Dr, Fort Bragg, CA 95437; or call (707) 961-1234.

PHYSICIANS WANTED

LONGVIEW, WASHINGTON



Longview is a picturesque, stable community of 42,000 located near the Columbia Gorge and the coastal mountains and beaches of Washington and Oregon. Members of our 12 physician group enjoy individual subpractices, infrequent call, and new state-of-the-art medical offices.

We invite you to contact us at the above address regarding practice opportunities. Or call Judy Parmenter, Physician Recruitment, (503) 280-2050 for further information.

BC/BE PEDIATRICIAN WANTED for semi-rural community 25 miles south of San Francisco to associate with five member Family Practice group. Send inquiry with CV to Lawrence Bruguera, MD, Coastside Medical Clinic, 225 S. Cabrillo Hwy, Ste 100-A, Half Moon Bay, CA 94019; (415) 726-0211.

GENERAL ORTHOPAEDIC SURGEON. Position for a BC/BE Orthopaedic Surgeon with a multispecialty 54 physician group practice. Experience must include partial and complete joint replacement. Join a practice with an established growth pattern in community of 120,000 plus, 40 minutes from downtown Sacramento. Marysville Medical Group was founded in 1938 and is the largest private practice group in rural northern California owned and governed by its own physicians. Send CV to Warren J. Boyer, MD, Medical Director, Marysville Medical Group, 800 Third St, Marysville, CA 95901.

OREGON. General Internal Medicine, BC/BE, sought for 10 member, multispecialty group in beautiful rural community, population 16,500, 38 miles southwest of Portland. Send CV to Administrator, 420 E. Fifth St, McMinnville, OR 97128; (503) 472-6161.

GERIATRICIAN/INTERNIST. We are seeking a BC Internist with Geriatric training or certification to join a group of two to practice Geriatric Medicine, actively participate in a university-affiliated teaching program, and assist in program development. Competitive salary and excellent fringe benefits. Send CV to Gary Steinke, MD, Santa Clara Valley Medical Center, 750 S. Bascom Ave, San Jose, CA 95128.

INFECTIOUS DISEASE PHYSICIAN, BE/BC, to join busy Internal Medicine/Cardiology practice one hour from Los Angeles. Excellent benefits. Send CV to Number 218, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

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Giving Physicians More Of What They Want

FHP® HEALTH CARE

(Continued on Page 458)

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PHYSICIANS WANTED

SAN FRANCISCO BAY AREA BC/BE INTERNISTS

We are currently seeking highly qualified Internists and subspecialists to complement our energetic Internal Medicine team. Department members provide a full range of medical services for a population of over 200,000 pre-paid health plan members. Recently renovated and expanded medical center facilities are within convenient commuting distance to virtually any bay area city, and the extensive cultural and recreational activities of northern California. As part of our large, multispecialty group practice, you would enjoy an excellent salary, generous fringe benefits, a flexible schedule, and the opportunity for academic affiliation with prestigious local institutions. Send CV to:

Winslow Wong, MD
Attn: Administration
Kaiser Permanente Medical Center
27400 Hesperian Blvd
Hayward, CA 94545
EOE

CALIFORNIA—SAN JOSE. Director wanted for hospital-based Walk-In Clinic with 30,000 annual visits. Applicants should have prior administrative experience and be BC/BE in a primary care specialty. Excellent compensation including fee-for-service, administrative compensation, and performance bonus. Please reply to Nanette Peter, Associated Emergency Physicians, Inc, 1625 The Alameda, Ste 201, San Jose, CA 95126; (408) 293-8881.

BC/BE NORTHWESTERN CALIFORNIA. OB/GYN needed to join the oldest office in the Redwood area on the north coast. An excellent opportunity for a male or female American trained physician. Excellent compensation and incentive program leading to corporate membership in one year. Three physicians in office but only two doing obstetrics. Send CV and references to T. W. Loring, MD, 2607 Harris St, Ste E, Eureka, CA 95501; (707) 442-4593.

SAN FRANCISCO EAST BAY. BE/BC Internist needed to join ten physician Primary Care group practice in beautiful San Ramon Valley area. Excellent opportunity and compensation. Reply in confidence to Number 223, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

BC/BE FAMILY PRACTITIONER to enjoy rural living with urban culture 20 minutes away. Generous vacation time to use the many nearby recreational opportunities. Join another Family Practitioner and two Physician Assistants in a Family Practice satellite of a large multispecialty clinic. Contact Jerry Corn, MD: (206) 687-5108 or Karen Stanton; (206) 254-1240.

ORTHOPEDIC SURGEON-SPORTS MEDICINE. To perform Arthroscopic procedures of all joints. Duties to include three-dimensional motion analysis of Anterior Cruciate Ligament Insufficiency, functional testing of braces for the Anterior Cruciate Ligament Deficient Knee, derotation of braces, radiologic evaluation of Chondromalacia Patella, correction or prevention of skeletal abnormalities, and sports injuries utilizing surgical, medical and physical methodologies. Requires a Doctor of Medicine and two years fellowship training in Sports Medicine. Must be Board Certified or be a member of The Royal College of Physicians and Surgeons of Canada or equivalent. Must have a California license. Must have experience in treating sports related injuries. Must have achieved academic recognition for work in sports injury and treatment through publication of research papers and being a speaker at medical conferences or symposiums. Pay is $110,000 per year. Job site and interview Fountain Valley, California. Send this ad and résumé to Job Number BLW 17504, PO Box 9560, Sacramento, CA 95823-0560, not later than November 10, 1990.

PHYSICIANS WANTED

IMMEDIATE OPENINGS

General Surgeon
◆◆◆
Family Practice
◆◆◆
Internal Medicine

In Northern Arizona lake country. Guaranteed salary plus bonus; unlimited earning power; ownership potential. Stable, 14-year-old private group practice. Call Marian Parry collect at (602) 645-8823 or FAX CV to (602) 645-2524.

COASTAL CALIFORNIA 45,000 population. Well-trained 12 physician primary care group. Immediate/future need for Family Practice and Internal Medicine. Competitive salary and benefits with partnership after one year. On call schedule allows time for family and recreation. In Lompoc, you can do what you were trained to do, including OB, Pediatrics, and General Medicine. Please contact Ken Baker, President, Physician Search Group, 120 Montgomery St, Ste 710, San Francisco, CA 94104; (415) 399-8840.

OB/GYN—BC/BE. Position with a multispecialty 54 physician group practice. Join five BC OB/GYN physicians in a practice with an established growth pattern in community of 120,000 plus. Marysville Medical Group was founded in 1938 and is the largest private practice group in rural northern California, owned and governed by its own physicians. Send CV to Warren J. Boyer, MD, Medical Director, Marysville Medical Group, 800 Third St, Marysville, CA 95901.

CENTRAL CALIFORNIA. Hospital based teaching opportunity for OB/GYN in a new Residency Program at the KMC. Ideal candidate is a team player with a strong desire to teach residents. This UCLA affiliate has a busy OB department with 5,000 deliveries per year. Please contact Mary Letterii, Vice President, Physicians Search Group, 120 Montgomery St, Ste 710, San Francisco, CA 94104; (415) 399-8840.

SOUTHERN CALIFORNIA. Young Family Practitioner with dynamic practice seeking associate for future partnership. Generous salary/guarantee and incentives package. New medical office near outstanding 300-bed community hospital. Growing community within one hour of beaches and mountains. Ken Baker, PSG, 120 Montgomery St, Ste 710, San Francisco, CA 94104; (415) 399-8840.

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PHYSICIANS WANTED

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Portland, OR 97227.
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23 PHYSICIAN GROUP PRACTICE. Recent population growth and demand have created the need for several specialists including OB/GYN, Cardiology, and Pediatrics in this 23 physician group practice. Situated 60 miles east of San Francisco, the group serves a local population of 35,000. Nearby skiing and boating, reasonable housing, and an excellent school system. Please contact Mary Letterii, Vice President, Physicians Search Group, 120 Montgomery St, Ste 710, San Francisco, CA 94104; (415) 399-8840.

OCCUPATIONAL MEDICINE, SAN FRANCISCO BAY AREA. Area's leading multispecialty private group practice is seeking BC/BE physician to join their expanding Department of Occupational Medicine. Range of practice includes pre-employment physicals, diagnostic evaluations, treatment of on-the-job injuries; comprehensive knowledge of all areas of Occupational Medicine. Competitive salary, plus incentive, excellent benefits, paid malpractice. Located in the South Bay which offers wonderful cultural/recreational activities, fine dining, outstanding climate and scenery, easy access to beach and mountains. For further information, please send CV or contact Maureen Forrester, San Jose Medical Group, Inc, 45 S. 17th St, San Jose, CA 95112.

ORTHOPEDIC SURGEONS. BC/BE sought for expanding group in Sacramento. Currently seeking experienced hand/upper extremity, spine, and general Orthopedists. Excellent growth and compensation potential. Limited call schedule, flexible hours, med/legal evaluations. Send CV to Number 214, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

NORTHERN CALIFORNIA. Immediate openings for Emergency, Family Practice, and General Internal Medicine physicians who desire to work in the wine country north of San Francisco. Positions available in moderate volume emergency departments and Ambulatory Care Center. A unique opportunity is also available for Family Practice and Internal Medicine physicians who desire to practice Inpatient Medicine without the hassles of an office practice. Guaranteed $90-$110,000 per year; paid malpractice. Contact Richard Gillespie, MD, Quantum Emergency Medical Associates, PO Box 2467, Santa Rosa, CA 95405; (707) 546-4199.

(Continued on Page 459)

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PHYSICIANS WANTED

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Join our rapidly expanding and well established multi-specialty group practice in Southern California. It's the ideal environment for physicians who are seeking a small community atmosphere, combined with the latest medical resources and technology of a major force in the health care industry.

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EDUCATION/PREVENTION COORDINATOR. Assist Director of Community Education in preparing lectures, articles and other educational material on communicative diseases and prevention. Present same to Spanish community. Require MD or MA in Public Health, six months experience and fluent Spanish. $2,925 per month. Job and interview in Los Angeles. Send this ad and résumé to Job Number DC-17353, PO Box 9560, Sacramento, CA 95823-0560, no later than November 15, 1990.

RADIOLOGIST. Major Los Angeles Radiology group is seeking a well-rounded general Radiologist with five to ten years experience to fill unexpected vacancy. Excellent first year salary, early partnership offered. Position involves directorship of an area hospital. Physician must be current and able to perform basic angiography and interventive procedure. Reply to Number 221, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

NONINVASIVE CARDIOLOGIST. Seeking well qualified noninvasive Cardiologist to join high volume single specialty two member group practice in scenic northern California. Salary guarantee and incentives, with partnership at two years. Send CVs to PO Box 1564, Cottonwood, CA 96022.

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CARDIOLOGIST
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Director of Ambulatory Care
San Luis Obispo General Hospital
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San Luis Obispo, CA 93403-8113

(805) 549-4936

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PHYSICIAN OPPORTUNITIES NATIONWIDE
For all specialities for hospitals, clinics, multi-specialty groups, partnership and solos. Contact Jim Grant in complete confidence at the bay area specialists. **Nugent & Grant, Inc, 1400 Coleman, Ste B-22, Santa Clara, CA 95090; or call (800) 727-2478, FAX # (408) 727-7390.** Never a fee to the physician.

CARDIOLOGIST—INVASIVE/NONINVASIVE BE/BC, to join four member busy Cardiology practice in small town, one hour from Los Angeles. Full range of noninvasive Cardiology and active Cath Lab. Position available immediately. Send CV to Number 218, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

OB/GYN. BC/BE to join expanding multispecialty group practice as third Obstetrician. Competitive salary, benefit package with potential for partnership status. Desirable southwest metropolitan area. Send inquiries to Larry Levey, Administrator, Tucson Medical Associates, 116 N. Tucson Blvd, Tucson, AZ 85716; (602) 327-5531.

INTERNAL MEDICINE. BC/BE to join expanding multispecialty group practice. Competitive salary, benefit package with potential for partnership status. Desirable southwest metropolitan area. Send inquiries to Larry Levey, Administrator, Tucson Medical Associates, 116 N. Tucson Blvd, Tucson, AZ 85716; (602) 327-5531.

EMERGENCY MEDICINE UNIVERSITY POSITION. The University of California, Davis, School of Medicine, is recruiting for a full-time faculty. The position will be at the Assistant or Associate Professor level. The Division of Emergency Medicine and Clinical Toxicology is undergoing rapid academic development and has an approved residency program in Emergency Medicine. The UCDMC Emergency Department provides comprehensive emergency service and is a major trauma center in northern California. The Department is a Paramedic Base Station and Training Center, and in addition, has an active Helicopter Service and Regional Poison Center. Candidates must be BC/BE in Emergency Medicine and be eligible for licensure in California. A letter outlining teaching background, interests, experience, and research in addition to a CV and the names of five references should be sent to Robert W. Derlet, MD, Chair, Emergency Medicine Search Committee, Tr 1219, University of California, Davis, Medical Center, 2315 Stockton Blvd, Sacramento, CA 95817. Applications will not be accepted after December 31, 1990. The University of California is an Affirmative Action/Equal Opportunity Employer.

ORTHOPEDIC SURGEON. Immediate opening available for associate Orthopedic Surgeon. Established Orthopedic Practice in North Hollywood, close to St. Joseph Medical Center. For information call office manager Lizzy Regester (818) 506-0999.

SAN FRANCISCO. Primary Care Practice in Noe Valley seeks BC/BE Family Practitioner or Internist to join growing practice. Competitive salary, wonderful neighborhood, partnership option. Send résumé to Noe Valley Family Medicine, 3700 24th St, San Francisco, CA 94114.

FAMILY PRACTICE RESIDENCY FACULTY POSITION—CASPER, WYOMING. University of Wyoming Family Practice Residency-Casper is seeking an experienced, clinically oriented, BC Pediatrician to be the Pediatric Coordinator of an 8-8-8 Family Practice residency program. Level II Nursery skills are a must. 60% teaching, 20% direct patient care, 20% research. This is a tenure track position. University approval will be required prior to filling this position. Come join us in beautiful Wyoming. The University of Wyoming is an affirmative action/EOE. Contact Dr David Driggers, Director, University of Wyoming Family Practice Residency, 1522 E. "A" St, Casper, WY 82601; (307) 266-3076.

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PHYSICIANS WANTED

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California Biotechnology is an innovative biopharmaceutical company engaged in the development of novel human therapeutics. In addition to an attractive compensation and benefits package, we are located in a desirable community in the San Francisco bay area.

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LOOKING FOR A PRIMARY CARE Internal Medicine Geriatric position with challenging and appreciative patients, quality associates, tolerable schedules in an attractive community? Send CV to Julie A. Prazich, MD, Medical Director, Sharp Senior HealthCare, 3545 Fourth Ave, San Diego, CA 92103.

GASTROENTEROLOGIST. Position for a BC/BE Gastroenterologist with a multispecialty 54 physician group practice. Certified Endoscopy unit and complete in-house Radiology and Nuclear Medicine. Join a practice with an established growth pattern in community of 120,000 plus. Marysville Medical Group was founded in 1938 and is the largest private practice group in rural northern California owned and governed by its own physicians. Send CV to Warren J. Boyer, MD, Medical Director, Marysville Medical Group, 800 Third St, Marysville, CA 95901.

ORANGE COUNTY. FAMILY PRACTICE OPPORTUNITIES. Physician groups associated with Brea Community Hospital are recruiting Primary Care Physicians, for solo or group practice opportunities. Send your résumé to Garry Donesky, Associate Administrator. Brea Community Hospital, 380 W. Central Ave, Brea, CA 92621; or call (714) 529-0211.

BC RADIOLOGIST. Position with a multispecialty 54 physician group practice—no hospital. Expertise in conventional diagnostic Radiology, Ultrasound, Mammography, Nuclear Medicine, CAT, and Uroradiology. Three Radiologists, with a staff of 14, do approximately 55,000 procedures annually. Marysville Medical Group was founded in 1938 and is the largest private practice group in rural northern California owned and governed by its own physicians. Send CV to Warren J. Boyer, MD, Medical Director, Marysville Medical Group, 800 Third St, Marysville, CA 95901.

PHYSICIANS WANTED

BOARD CERTIFIED FAMILY PHYSICIAN wanted to join two others within larger multispecialty practice in Kauai. OB preferred. Send CV to Drs Clay and Ratliff at 4366 Kukui Grove St, Ste 201, Lihue, HI 96766; or call (808) 245-4600.

CALIFORNIA, DANVILLE. Excellent opportunity for Family Practice Physician in established Family Practice/Urgent Care Center. 1,000 patients per month, no night call, no overhead, fee-for-service with minimum guarantee. Equity position available. Office located within residential community less than one hour from San Francisco, three hours from Lake Tahoe. Real estate values appreciating, commute only 10 minutes from the office. Tired of being put on salary? Able to perform flexible fiberoptic sigmoidoscopy, repair limited to complex lacerations, apply casts (fiberglass or plaster), excise benign lesions, perform treadmill exams, etc.? This position allows you to bill and receive accordingly. Malpractice paid. Send CV to Administrator, Danville Immediate Care Center Medical Group, 319 Diablo Rd, Ste 105, Danville, CA 94526.

GENERAL INTERNIST. The VA Medical Center, Long Beach, California is recruiting for a Staff Physician. Duties include seeing patients in Walk-in Clinic, supervision, and teaching of housestaff in clinic. VAMC Long Beach is affiliated with the College of Medicine at University of California, Irvine. Vacancy is full-time position, 40 hours per week. United States citizenship required. Please send CV to David Webb, MD, Associate Chief of Staff, Ambulatory Care (153), VA Medical Center, 5901 E. 7th St, Long Beach, CA 90822; or call (213) 494-5406. Equal Opportunity Employer.

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American Red Cross

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Ad Council

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PRACTICES AVAILABLE

SAN DIEGO COUNTY. Family, Internal, OB/GYN and Pediatric practices available. Long established—doctors retiring. Various prices and low down payments. Call CBI, San Diego County's professional practice sales specialists, (619) 283-7009.

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SAN FRANCISCO BAY AREA. Pain management practice. Excellent staff and administration. Opportunity for Internist, Psychiatrist, Family Practitioner, Neurologist, or partnership interested in pain or psychosomatic medicine. Reply to Number 208, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

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EIGHTH ANNUAL ADVANCES IN HEART DISEASE

December 7-9, 1990. San Francisco, California. Fees: $390 for ACC members; $455 for non-members; $245 for residents, fellows-in-training, nurses and technicians. 16 Category 1 Credit hours. For information, call **American College of Cardiology (800) 253-4636, in Maryland (301) 897-5400, ext 228.**

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January 31-February 2, 1991

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California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 8-13, 1991, Bally's Grand Hotel, Reno.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 13-16, 1990, Keystone.

Hawaii Medical Association—1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: October 12-14, 1990, Ilikai, Honolulu.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: 1991, date and location to be announced.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 4-6, 1990, Sheraton, Billings.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 25-28, 1991, Quail Lodge, Carmel, California.

New Mexico Medical Society—7770 Jefferson, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: 1991, date and location to be announced.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting (House of Delegates only): 1991, date and location to be announced.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 12-14, 1990, Marriott Hotel, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: September 20-23, 1990, Sheraton, Spokane.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: 1991, date and location to be announced.

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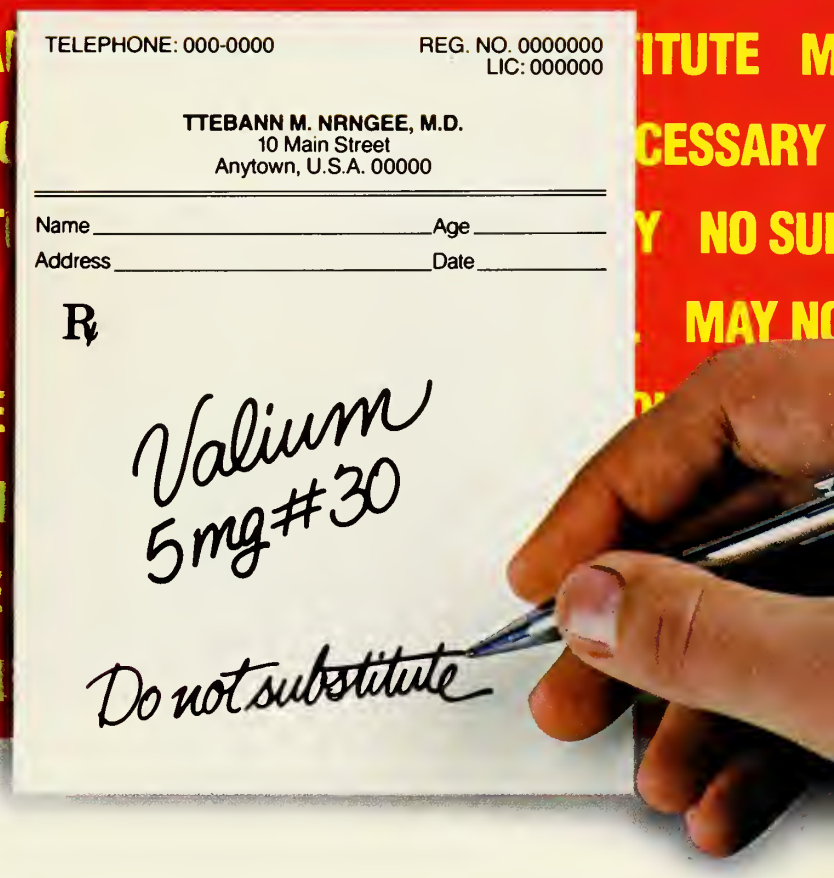

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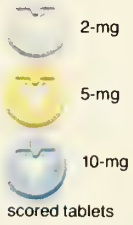

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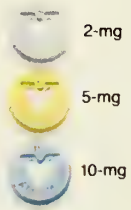

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Trental® (pentoxifylline) Tablets, 400 mg
A brief summary of the Prescribing Information follows.

INDICATIONS AND USAGE:
Trental® (pentoxifylline) is indicated for the treatment of patients with intermittent claudication on the basis of chronic occlusive arterial disease of the limbs. Trental® (pentoxifylline) can improve function and symptoms but is not intended to replace more definitive therapy, such as surgical bypass, or removal of arterial obstructions when treating peripheral vascular disease.

CONTRAINDICATIONS:
Trental® (pentoxifylline) should not be used in patients who have previously exhibited intolerance to this product or methylxanthines such as caffeine, theophylline, and theobromine.

PRECAUTIONS:
General: Patients with chronic occlusive arterial disease of the limbs frequently show other manifestations of arteriosclerotic disease. Trental® (pentoxifylline) has been used safely for treatment of peripheral arterial disease in patients with concurrent coronary artery and cerebrovascular diseases, but there have been occasional reports of angina, hypotension, and arrhythmia. Controlled trials do not show that Trental® (pentoxifylline) causes such adverse effects more often than placebo, but, as it is a methylxanthine derivative, it is possible some individuals will experience such responses.
Drug Interactions: Although a causal relationship has not been established, there have been reports of bleeding and/or prolonged prothrombin time in patients treated with Trental® (pentoxifylline) with and without anticoagulants or platelet aggregation inhibitors. Patients on warfarin should have more frequent monitoring of prothrombin times, while patients with other risk factors complicated by hemorrhage (e.g., recent surgery, peptic ulceration) should have periodic examinations for bleeding including hematocrit and/or hemoglobin. Trental® (pentoxifylline) has been used concurrently with antihypertensive drugs, beta blockers, digitalis, diuretics, antidiabetic agents, and antiarrhythmics, without observed problems. Small decreases in blood pressure have been observed in some patients treated with Trental® (pentoxifylline); periodic systemic blood pressure monitoring is recommended for patients receiving concomitant antihypertensive therapy. If indicated, dosage of the antihypertensive agents should be reduced.
Carcinogenesis, Mutagenesis and Impairment of Fertility: Long-term studies of the carcinogenic potential of pentoxifylline were conducted in mice and rats by dietary administration of the drug at doses up to approximately 24 times (570 mg/kg) the maximum recommended human daily dose (MRHD) of 24 mg/kg for 18 months in mice and 18 months in rats with an additional 6 months without drug exposure in the latter. No carcinogenic potential for pentoxifylline was noted in the mouse study. In the rat study, there was a statistically significant increase in benign mammary fibroadenomas in females in the high dose group (24 × MRHD). The relevance of this finding to human use is uncertain since this was only a marginal statistically significant increase for a tumor that is common in aged rats. Pentoxifylline was devoid of mutagenic activity in various strains of *Salmonella* (Ames test) when tested in the presence and absence of metabolic activation.
Pregnancy: Category C. Teratogenic studies have been performed in rats and rabbits at oral doses up to about 25 and 10 times the maximum recommended human daily dose (MRHD) of 24 mg/kg, respectively. No evidence of fetal malformation was observed. Increased resorption was seen in rats at 25 times MRHD. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Trental® (pentoxifylline) should be used during pregnancy only if clearly needed.
Nursing Mothers: Pentoxifylline and its metabolites are excreted in human milk. Because of the potential for tumorigenicity shown for pentoxifylline in rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.
Pediatric Use: Safety and effectiveness in children below the age of 18 years have not been established.

ADVERSE REACTIONS:
Clinical trials were conducted using either controlled-release Trental® (pentoxifylline) tablets for up to 60 weeks or immediate-release Trental® (pentoxifylline) capsules for up to 24 weeks. Dosage ranges in the tablet studies were 400 mg bid to tid and in the capsule studies, 200-400 mg tid.
The table summarizes the incidence (in percent) of adverse reactions considered drug related, as well as the numbers of patients who received controlled-release Trental® (pentoxifylline) tablets, immediate-release Trental® (pentoxifylline) capsules, or the corresponding placebos. The incidence of adverse reactions was higher in the capsule studies (where dose related increases were seen in digestive and nervous system side effects) than in the tablet studies. Studies with the capsule include domestic experience, whereas studies with the controlled-release tablets were conducted outside the U.S. The table indicates that in the tablet studies few patients discontinued because of adverse effects.

INCIDENCE (%) OF SIDE EFFECTS

	Controlled-Release Tablets		Immediate-Release Capsules	
	Commercially Available		Used only for Controlled Clinical Trials	
	Trental®	Placebo	Trental®	Placebo
(Numbers of Patients at Risk)	(321)	(128)	(177)	(138)
Discontinued for Side Effect	3.1	0	9.6	7.2
CARDIOVASCULAR SYSTEM				
Angina/Chest Pain	0.3	—	1.1	2.2
Arrhythmia/Palpitation	—	—	1.7	0.7
Flushing	—	—	2.3	0.7
DIGESTIVE SYSTEM				
Abdominal Discomfort	—	—	4.0	1.4
Belching/Flatus/Bloating	0.6	—	9.0	3.6
Diarrhea	—	—	3.4	2.9
Dyspepsia	2.8	4.7	9.6	2.9
Nausea	2.2	0.8	28.8	8.7
Vomiting	1.2	—	4.5	0.7
NERVOUS SYSTEM				
Agitation/Nervousness	—	—	1.7	0.7
Dizziness	1.9	3.1	11.9	4.3
Drowsiness	—	—	1.1	5.8
Headache	1.2	1.6	6.2	5.8
Insomnia	—	—	2.3	2.2
Tremor	0.3	0.8	—	—
Blurred Vision	—	—	2.3	1.4

Trental® (pentoxifylline) has been marketed in Europe and elsewhere since 1972. In addition to the above symptoms, the following have been reported spontaneously since marketing or occurred in other clinical trials with an incidence of less than 1%, the causal relationship was uncertain:
Cardiovascular—dyspnea, edema, hypotension.
Digestive—anorexia, cholecystitis, constipation, dry mouth/thirst.
Nervous—anxiety, confusion.
Respiratory—epistaxis, flu-like symptoms, laryngitis, nasal congestion.
Skin and Appendages—brittle fingernails, pruritus, rash, urticaria, angioedema.
Special Senses—blurred vision, conjunctivitis, earache, scotoma.
Miscellaneous—bad taste, excessive salivation, leukopenia, malaise, sore throat/swollen neck glands, weight change.
A few rare events have been reported spontaneously worldwide since marketing in 1972. Although they occurred under circumstances in which a causal relationship with pentoxifylline could not be established, they are listed to serve as information for physicians: Cardiovascular—angina, arrhythmia, tachycardia; Digestive—hepatitis, jaundice, increased liver enzymes; and Hemic and Lymphatic—decreased serum fibrinogen, pancytopenia, aplastic anemia, purpura, thrombocytopenia.

OVERDOSAGE:
Overdosage with Trental® (pentoxifylline) has been reported in children and adults. Symptoms appear to be dose related. A report from a poison control center on 44 patients taking overdoses of enteric-coated pentoxifylline tablets noted that symptoms usually occurred 4-5 hours after ingestion and lasted about 12 hours. The highest amount ingested was 80 mg/kg; flushing, hypotension, convulsions, somnolence, loss of consciousness, fever, and agitation occurred. All patients recovered.
In addition to symptomatic treatment and gastric lavage, special attention must be given to supporting respiration, maintaining systemic blood pressure, and controlling convulsions. Activated charcoal has been used to adsorb pentoxifylline in patients who have overdosed.

DOSAGE AND ADMINISTRATION:
The usual dosage of Trental® (pentoxifylline) in controlled-release tablet form is one tablet (400 mg) three times a day with meals.
While the effect of Trental® (pentoxifylline) may be seen within 2 to 4 weeks, it is recommended that treatment be continued for at least 8 weeks. Efficacy has been demonstrated in double-blind clinical studies of 6 months duration.
Digestive and central nervous system side effects are dose related. If patients develop these side effects it is recommended that the dosage be lowered to one tablet twice a day (800 mg/day). If side effects persist at this lower dosage, the administration of Trental® (pentoxifylline) should be discontinued. Edition 2/88
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(pentoxifylline)

The only proven-effective agent for intermittent claudication, a symptom of peripheral arterial disease

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While patients might feel somewhat better within weeks, at least 3 months' therapy is generally required before the full effectiveness of Trental® becomes evident. To sustain improvement, therapy must be continued.

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The subscription price per year is $35 in the United States and Canada (US funds); $60 in all other countries. Single copies are $5.00. USA/CANADA postage and handling included. All other countries add US $4.23 Air Printed Matter Postage. Address all subscription communications to:

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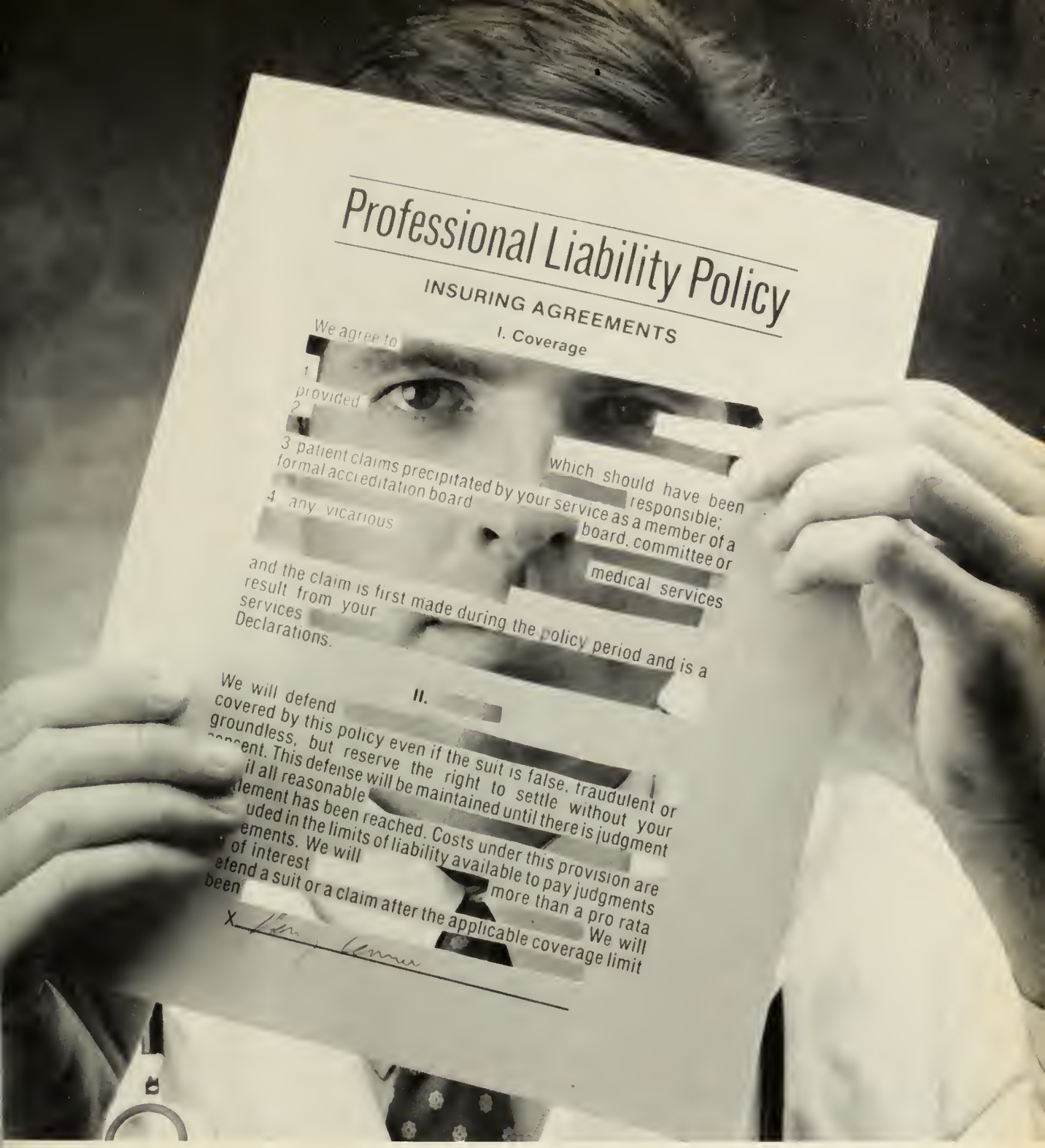
The Western Journal of Medicine

(ISSN 0093-0415/USPS 084 480) is published monthly for $35 per year (USA and Canada) by the California Medical Association, 221 Main Street, San Francisco, CA 94105. Second-class postage paid at San Francisco and additional mailing offices.

POSTMASTER: Send address changes to *The Western Journal of Medicine*, Circulation, PO Box 7602, San Francisco, CA 94120-7602.



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Brief Summary

DESCRIPTION: Azmacort (triamcinolone acetonide) is an anti-inflammatory steroid

INDICATIONS: Azmacort (triamcinolone acetonide) inhaler is indicated only for patients who require chronic treatment with corticosteroids for the control of the symptoms of bronchial asthma. Such patients would include those already receiving systemic corticosteroids and selected patients who are inadequately controlled on a non-steroid regimen and in whom steroid therapy has been withheld because of concern over potential adverse effects.

Azmacort inhaler is *NOT* indicated:

1. For relief of asthma which can be controlled by bronchodilators and other non-steroid medications.
2. In patients who require systemic corticosteroid treatment infrequently
3. In the treatment of non-asthmatic bronchitis.

CONTRAINDICATIONS: Azmacort inhaler is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required

Hypersensitivity to any of the ingredients of this preparation contraindicates its use.

WARNINGS: Particular care is needed in patients who are transferred from systemically active corticosteroids to Azmacort inhaler because deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to aerosolized steroids in recommended doses. After withdrawal from systemic corticosteroids, a number of months is usually required for recovery of hypothalamic-pituitary-adrenal (HPA) function. For some patients who have received large doses of oral steroids for long periods of time before therapy with Azmacort inhaler is initiated, recovery may be delayed for one year or longer. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery or infections, particularly gastroenteritis or other conditions with acute electrolyte loss. Although Azmacort inhaler may provide control of asthmatic symptoms during these episodes, in recommended doses it supplies only normal physiological amounts of corticosteroid systemically and does NOT provide the increased systemic steroid which is necessary for coping with these emergencies

During periods of stress or a severe asthmatic attack, patients who have been recently withdrawn from systemic corticosteroids should be instructed to resume systemic steroids (in large doses) immediately and to contact their physician for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic steroids during periods of stress or a severe asthma attack.

Localized infections with *Candida albicans* have occurred infrequently in the mouth and pharynx. These areas should be examined by the treating physician at each patient visit. The percentage of positive mouth and throat cultures for *Candida albicans* did not change during a year of continuous therapy. The incidence of clinically apparent infection is low (2.5%). These infections may disappear spontaneously or may require treatment with appropriate antifungal therapy or discontinuance of treatment with Azmacort inhaler.

Azmacort inhaler is not to be regarded as a bronchodilator and is not indicated for rapid relief of bronchospasm.

Patients should be instructed to contact their physician immediately when episodes of asthma which are not responsive to bronchodilators occur during the course of treatment with Azmacort inhaler. During such episodes, patients may require therapy with systemic corticosteroids.

There is no evidence that control of asthma can be achieved by the administration of Azmacort inhaler in amounts greater than the recommended doses, which appear to be the therapeutic equivalent of approximately 10 mg/day of oral prednisone.

Theoretically, the use of inhaled corticosteroids with alternate day prednisone oral therapy should be accompanied by more HPA suppression than a therapeutically equivalent regimen of either alone.

Transfer of patients from systemic steroid therapy to Azmacort inhaler may unmask allergic conditions previously suppressed by the systemic steroid therapy, e.g., rhinitis, conjunctivitis, and eczema.

PRECAUTIONS: During withdrawal from oral steroids, some patients may experience symptoms of systemically active steroid withdrawal, e.g., joint and/or muscular pain, lassitude and depression, despite maintenance or even improvement of respiratory function (See DOSAGE AND ADMINISTRATION for details). Although steroid withdrawal effects are usually transient and not severe, severe and even fatal exacerbation of asthma can occur if the previous daily oral corticosteroid requirement had significantly exceeded 10 mg/day of prednisone or equivalent.

In responsive patients, inhaled corticosteroids will often permit control of asthmatic symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since triamcinolone acetonide is absorbed into the circulation and can be systemically active, the beneficial effects of Azmacort inhaler in minimizing or preventing HPA dysfunction may be expected only when recommended dosages are not exceeded.

Suppression of HPA function has been reported in volunteers who received 4000 mcg daily of triamcinolone acetonide. In addition, suppression of HPA function has been reported in some patients who have received recommended doses for as little as 6-12 weeks. Since the response of HPA function to inhaled corticosteroids is highly individualized, the physician should consider this information when treating patients.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with these drugs should be observed carefully for any evidence of systemic corticosteroid effects including suppression of growth in children. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of a decrease in adrenal function.

The long-term effects of triamcinolone acetonide inhaler in human subjects are not completely known, although patients have received Azmacort inhaler on a continuous basis for periods of two years or longer. While there has been no clinical evidence of adverse experiences, the local effects of the agent on developmental or immunologic processes in the mouth, pharynx, trachea and lung are also unknown.

The potential effects of Azmacort inhaler on acute, recurrent, or chronic pulmonary infections, including active or quiescent tuberculosis, are not known. For this reason, since systemic administration of corticosteroids may mask some signs of fungal, bacterial or viral infection, the same caution should be observed when treating patients with Azmacort inhaler. The potential effects of long-term administration of Azmacort inhaler on lung or other tissues are unknown. However, pulmonary infiltrates with eosinophilia have occurred in patients receiving other inhaled corticosteroids.

Pregnancy: Pregnancy Category D: Azmacort (triamcinolone acetonide) has been shown to be teratogenic in rats and rabbits when given in doses comparable to the highest dose recommended for human use (approximately 0.032 mg/kg/day). Administration of aerosol inhalation to pregnant rats and rabbits produced embryotoxic and fetotoxic effects which were comparable to those produced by administration by other routes.

Teratogenic effects in both species included a low incidence of cleft palate and/or internal hydrocephaly and axial skeletal defects. These findings represent known effects of glucocorticoids in laboratory animals.

There are no well-controlled studies in pregnant women. Experience with other dosage forms of triamcinolone acetonide does not include any positive evidence of adverse effects on the fetus. However, since such experience cannot exclude possibility of fetal damage, Azmacort inhaler should be used during pregnancy only if the benefit clearly justifies the potential risk to the fetus. Infants born to mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for hypoadrenalism.

Nursing mothers: It is not known whether this drug is excreted in human milk. Because of the potential for tumorigenicity shown for triamcinolone acetonide in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

ADVERSE REACTIONS: A few cases of oral candidiasis have been reported (see WARNINGS). In addition, some patients receiving Azmacort inhaler have experienced hoarseness, dry throat, irritated throat and dry mouth. Increased wheezing and cough have been reported infrequently as has facial edema. These adverse effects have generally been mild and transient.

Caution: Federal (U.S.A.) law prohibits dispensing without prescription.

See Product circular for full prescribing information

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Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalmic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon® is indicated as a sympathicolytic and mydriatric. It may have activity as an aphrodisiac.

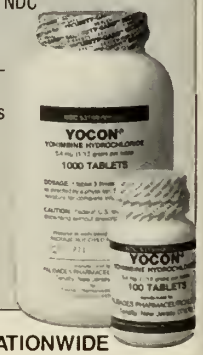
Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.[1,2] Also dizziness, headache, skin flushing reported when used orally.[1,3]

Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.[1,3,4] 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to ½ tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.[3]

How Supplied: Oral tablets of Yocon® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.



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References: 1. 1988 Joint National Committee: The 1988 report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med* 1988;148:1023-1038. **2.** *Physicians' Desk Reference®*, ed 44 Oradell, NJ, Medical Economics Company Inc, 1990.

BRIEF SUMMARY

Contraindications: Severe LV dysfunction (see *Warnings*), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), hypersensitivity to verapamil.

Warnings: Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol clearance may occur with combined use. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Concomitant use of lithium and verapamil may result in a lowering of serum lithium levels or increased sensitivity to lithium. Patients receiving both drugs must be monitored carefully. Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use.

Adverse Reactions: Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5%), headache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), bradycardia: HR < 50/min (1.4%), AV block: total 1°,2°,3° (1.2%), 2° and 3° (0.8%), rash (1.2%), flushing (0.6%), elevated liver enzymes. The following reactions, reported in 1.0% or less of patients, occurred under conditions where a causal relationship is uncertain: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gynecomastia, increased urination, spotty menstruation, impotence.

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From the Clinical Services, Graduate School of Public Health, College of Health and Human Services, San Diego State University, San Diego, California.

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MARK R. ROSENBERG, MD; MARIANNE PARSHLEY, MD; SCOTT GIBSON, MD; and RICHARD WERNICK, MD

From the Primary Care Training Program, Department of Medical Education, Providence Medical Center, and the Department of Medicine, Oregon Health Sciences University, Portland.

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‡Open-label trial. Diflucan 100 to 200 mg/day.
§Open-label, randomized trial. Clinical cure and improvement results. Diflucan 200 to 400 mg/day or amphotericin B 0.3 to 0.6 mg/kg/day.
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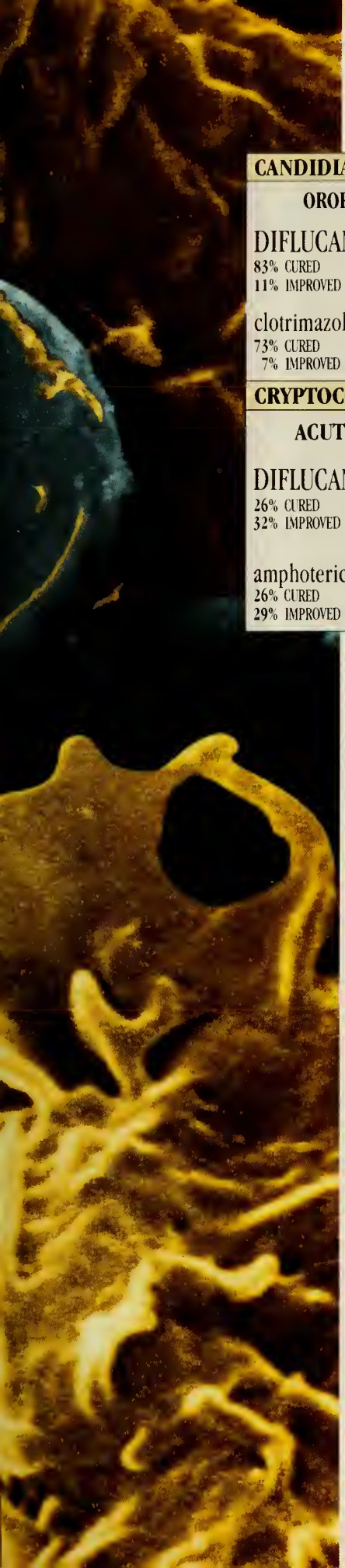

Excellent clinical success in oropharyngeal, esophageal, and systemic candidiasis, and cryptococcal meningitis:
Interim results from ongoing studies; due to the interim nature of these studies, statistics have not been provided.

CANDIDIASIS[1*]					
OROPHARYNGEAL[1*]		ESOPHAGEAL[1†] (endoscopic cures)		SYSTEMIC[1‡]	
DIFLUCAN 83% CURED 11% IMPROVED	94% (61/65)	DIFLUCAN	87% (20/23)	DIFLUCAN 63% CURED 23% IMPROVED	86% (189/219)
clotrimazole 73% CURED 7% IMPROVED	80% (36/45)	ketoconazole	53% (9/17)		

CRYPTOCOCCAL MENINGITIS			
ACUTE THERAPY[1§]		MAINTENANCE TO PREVENT RELAPSE[1‖]	
DIFLUCAN 26% CURED 32% IMPROVED	58% (54/93)	DIFLUCAN	98% (104/106)
amphotericin B 26% CURED 29% IMPROVED	55% (32/58)	amphotericin B	83% (64/77)

Excellent safety profile and patient compliance
In over 4,000 patients who received Diflucan for at least 7 days, the most common adverse events were nausea (3.7%), headaches (1.9%), and skin rash (1.8%).[1]

Rare incidence of serious hepatotoxicity has been reported, but the causal relationship to Diflucan is uncertain.[1]

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Oral bioavailability of Diflucan >90% and unaffected by agents that increase gastric pH.[1]

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INDICATION	FIRST DAY	DAILY THERAPY	MINIMUM DURATION OF THERAPY
OROPHARYNGEAL CANDIDIASIS:	200 mg	100 mg	14 days
ESOPHAGEAL CANDIDIASIS:	200 mg	100 mg*	21 days
SYSTEMIC CANDIDIASIS:	400 mg	200 mg	28 days
CRYPTOCOCCAL MENINGITIS (acute):	400 mg	200 mg*	10-12 weeks after CSF becomes culture negative
CRYPTOCOCCAL MENINGITIS (maintenance to prevent relapse):	200 mg	200 mg	

*Doses of up to 400 mg/day may be used based on medical judgement of the patient's response to therapy.

References: 1 Data on file, Roerig division of Pfizer Pharmaceuticals

INDICATIONS AND USAGE

DIFLUCAN (fluconazole) is indicated for the treatment of:

1 Oropharyngeal and esophageal candidiasis. DIFLUCAN is also effective for the treatment of serious systemic candidal infections, including urinary tract infection, peritonitis, and pneumonia

2 Cryptococcal meningitis

Specimens for fungal culture and other relevant laboratory studies (serology, histopathology) should be obtained prior to therapy to isolate and identify causative organisms. Therapy may be instituted before the results of the cultures and other laboratory studies are known, however, once these results become available, antiinfective therapy should be adjusted accordingly

CONTRAINDICATIONS

DIFLUCAN (fluconazole) is contraindicated in patients who have shown hypersensitivity to fluconazole or to any of its excipients. There is no information regarding cross hypersensitivity between fluconazole and other azole antifungal agents. Caution should be used in prescribing DIFLUCAN to patients with hypersensitivity to other azoles

WARNINGS

Patients who develop abnormal liver function tests during DIFLUCAN therapy should be monitored for the development of more severe hepatic injury. Although serious hepatic reactions have been rare and the causal association with DIFLUCAN uncertain, if clinical signs and symptoms consistent with liver disease develop that may be attributable to fluconazole, DIFLUCAN should be discontinued. (See Adverse Reactions.)

Immunocompromised patients who develop rashes during treatment with DIFLUCAN should be monitored closely and the drug discontinued if lesions progress. (See Adverse Reactions.)

PRECAUTIONS

Drug Interactions (See Clinical Pharmacology)

DIFLUCAN (fluconazole) increased the prothrombin time after warfarin administration. Careful monitoring of prothrombin time in patients receiving DIFLUCAN and coumarin-type anticoagulants is recommended.

DIFLUCAN increased the plasma concentrations of phenytoin. Careful monitoring of phenytoin concentrations in patients receiving DIFLUCAN and phenytoin is recommended.

DIFLUCAN has been infrequently associated with an increase in cyclosporine concentrations in renal transplant patients with or without impaired renal function. Careful monitoring of cyclosporine concentrations in patients receiving DIFLUCAN and cyclosporine is recommended.

DIFLUCAN increased the plasma concentrations and reduced the metabolism of tolbutamide, glyburide and glipizide. When DIFLUCAN is used concomitantly with these or other sulfonylurea oral hypoglycemic agents, blood glucose concentrations should be carefully monitored, and the dose of the sulfonylurea should be adjusted as necessary.

Rifampin enhances the metabolism of concurrently administered DIFLUCAN. Depending on clinical circumstances, consideration should be given to increasing the dose of DIFLUCAN when it is administered with rifampin.

Physicians should be aware that drug-drug interaction studies with other medications have not been conducted, but such interactions may occur.

Carcinogenesis, Mutagenesis and Impairment of Fertility

Fluconazole showed no evidence of carcinogenic potential in mice and rats treated orally for 24 months at doses of 2.5, 5 or 10 mg/kg/day (approximately 2-7x the recommended human dose). Male rats treated with 5 and 10 mg/kg/day had an increased incidence of hepatocellular adenomas.

Fluconazole, with or without metabolic activation, was negative in tests for mutagenicity in 4 strains of *S. typhimurium*, and in the mouse lymphoma L5178Y system. Cytogenetic studies *in vivo* (murine bone marrow cells, following oral administration of fluconazole) and *in vitro* (human lymphocytes exposed to fluconazole at 1000 μg/mL) showed no evidence of chromosomal mutations.

Fluconazole did not affect the fertility of male or female rats treated orally with daily doses of 5, 10 or 20 mg/kg or with parenteral doses of 5, 25 or 75 mg/kg, although the onset of parturition was slightly delayed at 20 mg/kg p.o. In an intravenous perinatal study in rats at 5, 20 and 40 mg/kg, dystocia and prolongation of parturition were observed in a few dams at 20 mg/kg (approximately 5-15x the recommended human dose) and 40 mg/kg, but not at 5 mg/kg. The disturbances in parturition were reflected by a slight increase in the number of stillborn pups and decrease of neonatal survival at these dose levels. The effects on parturition in rats are consistent with the species specific estrogen-lowering property produced by high doses of fluconazole. Such a hormone change has not been observed in women treated with fluconazole. (See Clinical Pharmacology.)

Pregnancy

Teratogenic Effects. Pregnancy Category C: Fluconazole was administered orally to pregnant rabbits during organogenesis in two studies, at 5, 10 and 20 mg/kg and at 5, 25, and 75 mg/kg respectively maternal weight gain was impaired at all dose levels, and abortions occurred at 75 mg/kg (approximately 20-60x the recommended human dose), no adverse fetal effects were detected. In several studies in which pregnant rats were treated orally with fluconazole during organogenesis, maternal weight gain was impaired and placental weights were increased at 25 mg/kg. There were no fetal effects at 5 or 10 mg/kg, increases in fetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25 and 50 mg/kg and higher doses. At doses ranging from 80 mg/kg (approximately 20-60x the recommended human dose) to 320 mg/kg embryolethality in rats was increased and fetal abnormalities included wavy ribs, cleft palate and abnormal craniofacial ossification. These effects are consistent with the inhibition of estrogen synthesis in rats and may be a result of known effects of lowered estrogen on pregnancy, organogenesis and parturition.

There are no adequate and well controlled studies in pregnant women. DIFLUCAN should be used in pregnancy only if the potential benefit justifies the possible risk to the fetus.

Nursing Mothers

It is not known whether fluconazole is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when DIFLUCAN is administered to a nursing woman.

Pediatric Use

Efficacy of DIFLUCAN has not been established in children. A small number of patients from age 3 to 13 years have been treated safely with DIFLUCAN using doses of 3-6 mg/kg daily.

ADVERSE REACTIONS

Sixteen percent of over 4000 patients treated with DIFLUCAN (fluconazole) in clinical trials of 7 days or more experienced adverse events. Treatment was discontinued in 1.5% of patients due to adverse clinical events and in 1.3% of patients due to laboratory test abnormalities.

In combined clinical trials and foreign marketing experience prior to U.S. marketing, patients with serious underlying disease (predominantly AIDS or malignancy) rarely have developed serious hepatic reactions or exfoliative skin disorders during treatment with DIFLUCAN (See Warnings). Two of these hepatic reactions and one exfoliative skin disorder (Stevens-Johnson syndrome) were associated with a fatal outcome. Because most of these patients were receiving multiple concomitant medications, including many known to be hepatotoxic or associated with exfoliative skin disorders, the causal association of these reactions with DIFLUCAN therapy is uncertain.

Clinical adverse events were reported more frequently in HIV infected patients (21%) than in non-HIV infected patients (13%), however, the patterns in HIV infected and non-HIV infected patients were similar. The proportions of patients discontinuing therapy due to clinical adverse events were similar in the two groups (1.5%).

The following treatment-related clinical adverse events occurred at an incidence of 1% or greater in 4048 patients receiving DIFLUCAN for 7 or more days in clinical trials: nausea 3.7%, headache 1.9%, skin rash 1.8%, vomiting 1.7%, abdominal pain 1.7%, and diarrhea 1.5%.

In two comparative trials evaluating the efficacy of DIFLUCAN for the suppression of relapse of cryptococcal meningitis, a statistically significant increase was observed in median AST (SGOT) levels from a baseline value of 30 IU/L to 41 IU/L in one trial and 34 IU/L to 66 IU/L in the other. The overall rate of serum transaminase elevations of more than 8 times the upper limit of normal was approximately 1% in fluconazole-treated patients in clinical trials. These elevations occurred in patients with severe underlying disease, predominantly AIDS or malignancies, most of whom were receiving multiple concomitant medications, including many known to be hepatotoxic. The incidence of abnormally elevated serum transaminases was greater in patients taking DIFLUCAN concomitantly with one or more of the following medications: rifampin, phenytoin, isoniazid, valproic acid, or oral sulfonylurea hypoglycemic agents.

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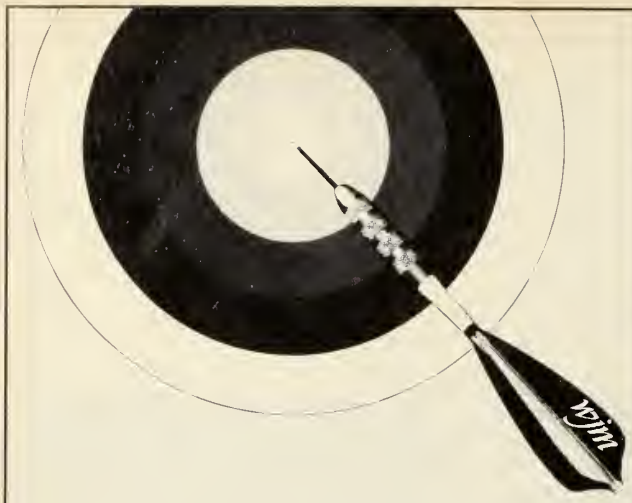

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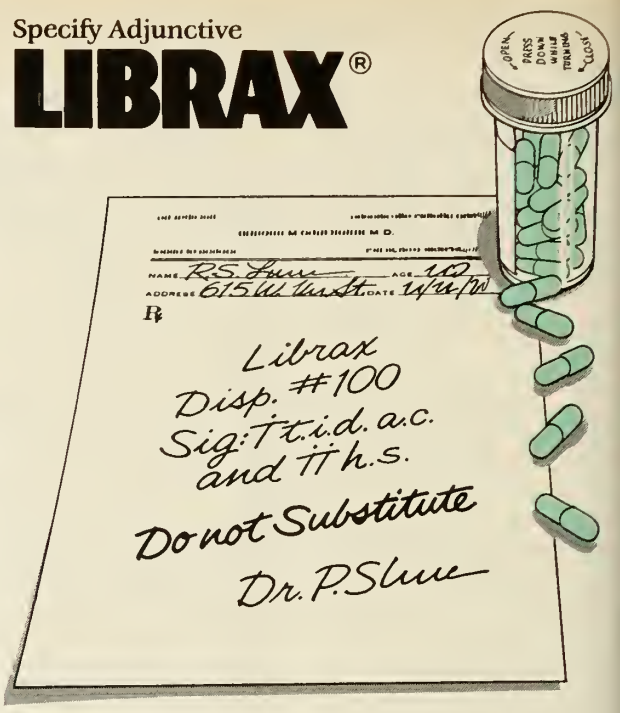

Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium bromide.

Please consult complete prescribing information, a summary of which follows:

* Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:
"Possibly" effective: as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.
Final classification of the less-than-effective indications requires further investigation.

Contraindications: Glaucoma; prostatic hypertrophy, benign bladder neck obstruction; hypersensitivity to chlordiazepoxide HCl and/or clidinium Br.
Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants, and against hazardous occupations requiring complete mental alertness (*e g*, operating machinery, driving).
Usage in Pregnancy: Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.
As with all anticholinergics, inhibition of lactation may occur.
Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).
Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established. Inform patients to consult physician before increasing dose or abruptly discontinuing this drug.
Adverse Reactions: No side effects or manifestations not seen with either compound alone reported with Librax. When chlordiazepoxide HCl is used alone, drowsiness, ataxia, confusion may occur, especially in elderly and debilitated; avoidable in most cases by proper dosage adjustment, but also occasionally observed at lower dosage ranges. Syncope reported in a few instances. Also encountered: isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent, generally controlled with dosage reduction; changes in EEG patterns may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice, hepatic dysfunction reported occasionally with chlordiazepoxide HCl, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax typical of anticholinergic agents, *i e*, dryness of mouth, blurring of vision, urinary hesitancy, constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.
Drug Abuse and Dependence: Withdrawal symptoms similar to those noted with barbiturates and alcohol have occurred following abrupt discontinuance of chlordiazepoxide; more severe seen after excessive doses over extended periods; milder after taking continuously at therapeutic levels for several months. After extended therapy, avoid abrupt discontinuation and taper dosage. Carefully supervise addiction-prone individuals because of predisposition to habituation and dependence.

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- Over 90% of angina patients controlled on nifedipine capsules were easily switched to and controlled on PROCARDIA XL Extended Release Tablets at the nearest equivalent total daily dose; others needed dosage adjustment[1]

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50–70 mg/day in divided doses	→ **60 mg once a day**
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- Subsequent dosage adjustments may be necessary and should be initiated as clinically warranted
- The total daily dose can be given with multiple tablets once a day, such as two 30-mg PROCARDIA XL Extended Release Tablets to equal 60 mg total daily dose
- Experience with doses > 90 mg in patients with angina is limited; therefore, doses > 90 mg should be used with caution and only when clinically warranted
- Low incidence of vasodilatory side effects. The most common side effects are peripheral edema, which is not associated with fluid retention, and headache

In controlled trials of 776 patients with PROCARDIA XL, edema resulted in discontinuation of therapy in 2.7% of patients[1]

Reference: 1. Data on file. Medical Department, Pfizer Labs, Pfizer Inc, New York

Brief Summary

PRDCARDIA XL® (nifedipine) Extended Release Tablets For Oral Use

CONTRAINDICATIONS: Known hypersensitivity reaction to nifedipine

WARNINGS: Excessive Hypotension: Although in most angina patients the hypotensive effect of nitedipine is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving nifedipine together with a beta-blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of nifedipine and a beta blocker, but the possibility that it may occur with nifedipine alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In nifedipine-treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for nifedipine to be washed out of the body prior to surgery

The following information should be taken into account in those patients who are being treated for hypertension as well as angina:

Increased Angina and/or Myocardial Infarction: Rarely, patients, particularly those who have severe obstructive coronary artery disease, have developed well documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting nifedipine or at the time of dosage increase. The mechanism of this effect is not established.

Beta Blocker Withdrawal: It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning nifedipine. Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of nitedipine treatment will not prevent this occurrence and on occasion has been reported to increase it.

Congestive Heart Failure: Rarely, patients usually receiving a beta blocker, have developed heart failure after beginning nifedipine. Patients with tight aortic stenosis may be at greater risk for such an event, as the unloading effect of nifedipine would be expected to be of less benefit to those patients, owing to their fixed impedance to flow across the aortic valve.

PRECAUTIONS: General—Hypotension: Because nifedipine decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of nifedipine is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See WARNINGS.)

Peripheral Edema: Mild to moderate peripheral edema occurs in a dose dependent manner with an incidence ranging from approximately 10% to about 30% at the highest dose studied (180 mg). It is a localized phenomenon thought to be associated with vasodilation of dependent arterioles and small blood vessels and not due to left ventricular dysfunction or generalized fluid retention. With patients whose angina or hypertension is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Other: As with any other non-deformable material, caution should be used when administering PROCARDIA XL in patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of PROCARDIA XL.

Laboratory Tests: Rare, usually transient, but occasionally significant elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted. The relationship to nitedipine therapy is uncertain in most cases, but probable in some. These laboratory abnormalities have rarely been associated with clinical symptoms; however, cholestasis with or without jaundice has been reported. A small (5.4%) increase in mean alkaline phosphatase was noted in patients treated with PROCARDIA XL. This was an isolated finding not associated with clinical symptoms and it rarely resulted in values which fell outside the normal range. Rare instances of allergic hepatitis have been reported. In controlled studies, PRDCARDIA XL did not adversely affect serum uric acid, glucose, or cholesterol. Serum potassium was unchanged in patients receiving PROCARDIA XL in the absence of concomitant diuretic therapy, and slightly decreased in patients receiving concomitant diuretics

Nifedipine, like other calcium channel blockers, decreases platelet aggregation *in vitro*. Limited clinical studies have demonstrated a moderate but statistically significant decrease in platelet aggregation and increase in bleeding time in some nifedipine patients. This is thought to be a function of inhibition of calcium transport across the platelet membrane. No clinical significance for these findings has been demonstrated.

Positive direct Coombs test with/without hemolytic anemia has been reported but a causal relationship between nifedipine administration and positivity of this laboratory test, including hemolysis, could not be determined.

Although nifedipine has been used safely in patients with renal dysfunction and has been reported to exert a beneficial effect in certain cases, rare reversible elevations in BUN and serum creatinine have been reported in patients with pre-existing chronic renal insufficiency. The relationship to nifedipine therapy is uncertain in most cases but probable in some.

Drug Interactions—Beta-adrenergic blocking agents. (See WARNINGS) Experience in over 1400 patients with Procardia® capsules in a noncomparative clinical trial has shown that concomitant administration of nifedipine and beta-blocking agents is usually well tolerated but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension, or exacerbation of angina.

Long Acting Nitrates: Nitedipine may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Digitalis: Administration of nifedipine with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing nitedipine to avoid possible over- or under-digitalization.

Coumarin Anticoagulants: There have been rare reports of increased prothrombin time in patients taking coumarin anticoagulants to whom nifedipine was administered. However, the relationship to nifedipine therapy is uncertain.

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak nifedipine plasma levels (80%) and area-under-the-curve (74%), after a one week course of cimetidine at 1000 mg per day and nifedipine at 40 mg per day. Ranitidine produced smaller, non-significant increases. The effect may be mediated by the known inhibition of cimetidine on hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of nifedipine. It nitedipine therapy is initiated in a patient currently receiving cimetidine, cautious titration is advised.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Nifedipine was administered orally to rats, for two years and was not shown to be carcinogenic. When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose. *In vivo* mutagenicity studies were negative.

Pregnancy: Pregnancy Category C. Nifedipine has been shown to be teratogenic in rats when given in doses 30 times the maximum recommended human dose. Nifedipine was embryotoxic (increased fetal resorptions, decreased fetal weight, increased stunted forms, increased fetal deaths, decreased neonatal survival) in rats, mice, and rabbits at doses of from 3 to 10 times the maximum recommended human dose. In pregnant monkeys, doses 2/3 and twice the maximum recommended human dose resulted in small placentas and underdeveloped chorionic villi. In rats, doses three times maximum human dose and higher caused prolongation of pregnancy. There are no adequate and well controlled studies in pregnant women. PRDCARDIA XL® (nifedipine) Extended Release Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

ADVERSE EXPERIENCES: Over 1000 patients from both controlled and open trials with PRDCARDIA XL Extended Release Tablets in hypertension and angina were included in the evaluation of adverse experiences. All side effects reported during PRDCARDIA XL Extended Release Tablet therapy were tabulated independent of their causal relation to medication. The most common side effect reported with PROCARDIA XL was edema which was dose related and ranged in frequency from approximately 10% to about 30% at the highest dose studied (180 mg). Other common adverse experiences reported in placebo-controlled trials include: headache (15.8%, compared to 9.8% placebo incidence), fatigue (5.9%, compared to 4.1% placebo incidence), dizziness (4.1%, compared to 4.5% placebo incidence), constipation (3.3%, compared to 2.3% placebo incidence), and nausea (3.3%, compared to 1.9% placebo incidence). Of these, only edema and headache were more common in PROCARDIA XL patients than placebo patients.

The following adverse reactions occurred with an incidence of less than 3.0%. With the exception of leg cramps, the incidence of these side effects was similar to that of placebo alone: *body as a whole/systemic*: asthenia, flushing, pain; *cardiovascular*: palpitations; *central nervous system*: insomnia, nervousness, paresthesia, somnolence; *dermatologic*: pruritus, rash; *gastrointestinal*: abdominal pain, diarrhea, dry mouth, dyspepsia, flatulence; *musculoskeletal*: arthralgia, leg cramps; *respiratory*: chest pain (nonspecific), dyspnea; *urogenital*: impotence, polyuria

Other adverse reactions were reported sporadically with an incidence of 1.0% or less. These include: *body as a whole/systemic*: face edema, fever, hot flashes, malaise, periorbital edema, rigors; *cardiovascular*: arrhythmia, hypotension, increased angina, tachycardia, syncope; *central nervous system*: anxiety, ataxia, decreased libido, depression, hypertonia, hypoesthesia, migraine, paronina, tremor, vertigo; *dermatologic*: alopecia, increased sweating, urticaria, purpura; *gastrointestinal*: eructation, gastroesophageal reflux, gum hyperplasia, melena, vomiting, weight increase; *musculoskeletal*: back pain, gout, myalgias; *respiratory*: coughing, epistaxis, upper respiratory tract infection, respiratory disorder, sinusitis; *special senses*: abnormal lacrimation, abnormal vision, taste perversion, tinnitus; *urogenital/reproductive*: breast pain, dysuria, hematuria, nocturia.

Adverse experiences which occurred in less than 1 in 1000 patients cannot be distinguished from concurrent disease states or medications.

The following adverse experiences, reported in less than 1% of patients, occurred under conditions (e.g., open trials, marketing experience) where a causal relationship is uncertain: gastrointestinal irritation, gastrointestinal bleeding.

In multiple-dose U.S. and foreign controlled studies with nitedipine capsules in which adverse reactions were reported spontaneously, adverse effects were frequent but generally not serious and rarely required discontinuation of therapy or dosage adjustment. Most were expected consequences of the vasodilator effects of Procardia. Adverse experiences reported in placebo-controlled trials include: dizziness, lightheadedness, and giddiness (27%, compared to 15% placebo incidence); flushing, heat sensation (25%, compared to 8% placebo incidence); headache (23%, compared to 20% placebo incidence); weakness (12%, compared to 10% placebo incidence); nausea, heartburn (11%, compared to 8% placebo incidence); muscle cramps, tremor (8%, compared to 3% placebo incidence), peripheral edema (7%, compared to 1% placebo incidence); nervousness, mood changes (7%, compared to 4% placebo incidence), palpitation (7%, compared to 5% placebo incidence): dyspnea, cough, and wheezing (6%, compared to 3% placebo incidence); and nasal congestion, sore throat (6%, compared to 8% placebo incidence)

There is also a large uncontrolled experience in over 2100 patients in the United States. Most of the patients had vasospastic or resistant angina pectoris, and about half had concomitant treatment with beta-adrenergic blocking agents. The relatively common adverse events were similar in nature to those seen with PROCARDIA XL.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

In a subgroup of over 1000 patients receiving Procardia with concomitant beta blocker therapy, the pattern and incidence of adverse experiences was not different from that of the entire group of Procardia treated patients (See PRECAUTIONS.)

In a subgroup of approximately 250 patients with a diagnosis of congestive heart failure as well as angina, dizziness or lightheadedness, peripheral edema, headache or flushing each occurred in one in eight patients. Hypotension occurred in about one in 20 patients. Syncope occurred in approximately one patient in 250. Myocardial infarction or symptoms of congestive heart failure each occurred in about one patient in 15. Atrial or ventricular dysrhythmias each occurred in about one patient in 150.

In post-marketing experience, there have been rare reports of exfoliative dermatitis caused by nitedipine

More detailed professional information available on request. Revised July 1990

Pfizer Labs

In Memoriam

California Medical Association

Andrews, Carroll B., Sonoma. Died Jul 11, 1990, aged 85. Graduate of Stanford University, 1932. Licensed in California in 1933. Dr Andrews was a member of the Sonoma County Medical Association.

Azimi, Jaleh, El Cajon. Died Jun 1990, aged 50. Graduate of Reperto Carola University, Heidelberg, West Germany, 1965. Licensed in California in 1986. Dr Azimi was a member of the San Diego County Medical Society.

Barrington, Sylvester, Hayward. Died Jul 2, 1990, aged 51. Graduate of Howard University, Washington, DC, 1964. Licensed in California in 1969. Dr Barrington was a member of the Alameda-Contra Costa Medical Association.

Blum, John, San Jose. Died Jun 20, 1990, aged 87. Graduate of University of California, San Francisco, 1936. Licensed in California in 1936. Dr Blum was a member of the Santa Clara County Medical Association.

Boris, Michael Z., San Francisco. Died Jun 15, 1990, aged 48. Graduate of Jefferson Medical College, Philadelphia, 1967. Licensed in California in 1968. Dr Boris was a member of the San Francisco Medical Society.

Dickstein, Leopold, Oakland. Died Jun 23, 1990, aged 75. Graduate of University of California, San Francisco, 1946. Licensed in California in 1946. Dr Dickstein was a member of the Alameda-Contra Costa Medical Association.

Dunlop, Russell, Coalinga. Died Aug 19, 1990, aged 61. Graduate of Manitoba Medical College, Winnepeg, Canada, 1956. Licensed in California in 1960. Dr Dunlop was a member of the Fresno-Madera Medical Society.

Gamble, John R., San Francisco. Died Jun 27, 1990, aged 68. Graduate of University of Pennsylvania School of Medicine, Philadelphia, 1951. Licensed in California in 1955. Dr Gamble was a member of the San Francisco Medical Society.

Goza, Samuel D., Fresno. Died Aug 15, 1990, aged 61. Graduate of St Louis University School of Medicine, 1955. Licensed in California in 1956. Dr Goza was a member of the Fresno-Madera Medical Society.

Grant, Dudley F. P., Hayward. Died Jul 31, 1990, aged 77. Graduate of Marquette University School of Medicine, 1943. Licensed in California in 1944. Dr Grant was a member of the Alameda-Contra Costa Medical Association.

Gump, Millard E., Oakland. Died Aug 25, 1990, aged 96. Graduate of University of Nebraska, Omaha, 1932. Licensed in California in 1938. Dr Gump was a member of the Alameda-Contra Costa Medical Association.

Jackson, Bruce W., Berkeley. Died Jun 18, 1990, aged 50. Graduate of Yale University, New Haven, Conn, 1966. Licensed in California in 1967. Dr Jackson was a member of the Alameda-Contra Costa Medical Association.

Jennings, Percy H., Berkeley. Died Jun 17, 1990, aged 82. Graduate of Harvard Medical College, Boston, 1934. Licensed in California in 1939. Dr Jennings was a member of the Alameda-Contra Costa Medical Association.

Kazato, Henry H., Fresno. Died Aug 21, 1990, aged 79. Graduate of University of California, San Francisco, 1940. Licensed in California in 1940. Dr Kazato was a member of the Fresno-Madera Medical Society.

Klaus, A. W., Visalia. Died Jun 1990, aged 81. Graduate of University of Tennessee, Memphis, 1940. Dr Klaus was a member of the Tulare County Medical Society.

Lage, Raleigh, Oakland. Died Jul 12, 1990, aged 78. Graduate of University of Iowa, Iowa City, 1937. Licensed in California in 1946. Dr Lage was a member of the Alameda-Contra Costa Medical Association.

Lawrence, Donald Jay, Yuba City. Died Aug 6, 1990, aged 59. Graduate of University of California, 1961. Licensed in California in 1962. Dr Lawrence was a member of the Yuba-Sutter-Colusa Medical Society.

Maas, Donald, W., Sacramento. Died Jun 18, 1990, aged 71. Graduate of Northwestern University, Chicago, 1943. Licensed in California in 1953. Dr Maas was a member of the Sacramento-El Dorado Medical Society.

McLaughlin, Joseph C., La Jolla. Died Aug 17, 1990, aged 67. Graduate of Temple University, Philadelphia. Licensed in California in 1958. Dr McLaughlin was a member of the San Diego County Medical Society.

Meehan, Carl W. J., Sacramento. Died Jun 10, 1990, aged 74. Graduate of St Louis University, 1940. Licensed in California in 1940. Dr Meehan was a member of the Sacramento-El Dorado Medical Society.

Millman, Milton, San Diego. Died Aug 19, 1990, aged 74. Graduate of New York College of Medicine, 1938. Licensed in California in 1947. Dr Millman was a member of the San Diego County Medical Society.

Naman, Marvin J., Santa Cruz. Died Jun 25, 1990, aged 71. Graduate of McGill University, Montreal, 1944. Licensed in California in 1947. Dr Naman was a member of the Santa Cruz County Medical Society.

Offield, Leonard D., Burlingame. Died Sep 5, 1990, aged 81. Graduate of Stanford University School of Medicine, 1939. Licensed in California in 1939. Dr Offield was a member of the San Mateo County Medical Society.

Roberts, Paul Curtis, Eureka. Died Jul 5, 1990, aged 77. Graduate of McGill Medical School, Montreal, 1939. Licensed in California in 1939. Dr Roberts was a member of the Humboldt-Del Norte Medical Society.

Saba, Richard Michael, San Diego. Died Jun 1990, aged 36. Graduate of University of Sherbrooke, Quebec, 1979. Licensed in California in 1982. Dr Saba was a member of the San Diego County Medical Society.

Sappinston, Edith, San Francisco. Died Jul 28, 1990, aged 91. Graduate of University of California, San Francisco, 1927. Licensed in California in 1930. Dr Sappinston was a member of the San Francisco Medical Society.

Schiller, Ian Michael, Sacramento. Died Jan 19, 1990, aged 47. Graduate of University of California, San Francisco, 1972. Licensed in California in 1973. Dr Schiller was a member of the Sacramento-El Dorado Medical Society.

Terwilliger, Calvin, San Francisco. Died Apr 17, 1990, aged 75. Graduate of Stanford University, Stanford, California, 1939. Dr Terwilliger was a member of the San Francisco Medical Society.

Trotta, Percy F., Oceanside. Died May 24, 1990, aged 62. Graduate of State University of New York, 1955. Licensed in California in 1970. Dr Trotta was a member of the San Diego County Medical Society.

Ver, Husen L., Jr, San Bernardino. Died Jul 17, 1990, aged 60. Graduate of UCLA Medical School, Los Angeles, 1960. Licensed in California in 1961. Dr Ver was a member of the San Bernardino County Medical Society.

Wilson, John C., San Jose. Died Jun 26, 1990, aged 83. Dr Wilson was a member of the Santa Clara County Medical Association.

Denver Medical Society

Wurtzebach, Lorenz Robert. Died Sep 10, 1990, aged 72. Graduate of University of Colorado, Denver, 1943. Licensed in Colorado in 1943.

New Mexico Medical Society

Anderson, Robert V., Roswell. Died Aug 5, 1990, aged 71. Graduate of Jefferson Medical College, Philadelphia, 1951. Licensed in New Mexico in 1966. Dr Anderson was a member of the Chaves County Medical Society.

Hoyt, Thomas W., Albuquerque. Died Sep 11, 1990, aged 49. Graduate of University of Washington, Seattle, 1966. Licensed in New Mexico in 1975. Dr Hoyt was a member of the Greater Albuquerque Medical Association.

Utah Medical Association

Rosenberg, Harold, Salt Lake City. Died Jun 20, 1990, aged 77. Graduate of Downstate Medical Center, New York, 1939. Licensed in Utah in 1953. Dr Rosenberg was a member of the Salt Lake County Medical Society.

Snow, Spencer, Salt Lake City. Died Aug 22, 1990, aged 88. Graduate of Rush School of Medicine, Chicago, 1933. Licensed in Utah in 1938. Dr Snow was a member of the Salt Lake County Medical Society.

Continuing Medical Education

ARIZONA • CALIFORNIA, HAWAII, NEVADA • COLORADO • IDAHO • NEW MEXICO • UTAH • WASHINGTON • WYOMING

ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

November 15-18—**Psychiatric Medicine in the '90s: The Emergence of Consultation/Liaison Psychiatry.** Academy of Psychosomatic Medicine, 37th Annual Meeting, at The Pointe—Squaw Peak, Phoenix. Thurs-Sun. Contact: (312) 784-2025.

November 16-17—**Techniques in Gynecologic Surgery.** Mayo Clinic-Scottsdale at Hyatt Regency Scottsdale at Gainey Ranch, Scottsdale. Fri-Sat. Contact: Jodi Lee Smith, (602) 391-7072.

November 17-18—**Obstetrical Pathology: POC, Placental and Perinatal Disorders.** Arizona Society of Pathologists at the Clarion Hotel, Scottsdale. Sat-Sun. Contact: Beverly Reichter, (602) 246-8901.

November 18-21—**7th Annual State of the Art in Total Joint Replacement.** Harrington Arthritis Research Center at Scottsdale Princess Resort, Scottsdale. Sun-Wed. Contact: Nancy Neroni, (602) 254-0377.

January 19—**Current Topics in Anesthesia.** Mayo Clinic-Scottsdale. Sat. Contact: Trish Gean, (602) 391-8300.

February 15-17—**Anesthesia for the 90s: 17th Annual Scientific Meeting.** Arizona Society of Anesthesiologists at Wyndham Paradise Valley Resort, Paradise Valley. Fri-Sun. Contact: Beverly Reichter, (602) 246-8901.

February 21-23—**17th Annual Frontiers in Ophthalmology.** St Luke's Medical Center at Red Lion's La Posada Resort, Scottsdale. Thurs-Sat. Contact: Christine Campbell, (602) 820-7027.

February 28-March 2—**13th Annual Postgraduate Course: Advances in Obstetrics and Gynecology.** Maricopa Medical Center and Phoenix OB/GYN Society at the Scottsdale Hilton Hotel, Scottsdale. Thurs-Sat. Contact: (602) 266-6321.

March 16-20—**Fifth Annual Magnetic Resonance Imaging Conference.** Barrow Neurological Institute at Marriott's Camelback Inn, Scottsdale. Sat-Wed. Contact: Kevin King, RT, (602) 285-3956.

CONTACT INFORMATION

ArMA—Contact. Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Jodi Lee Smith, Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 391-8300.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724 (602) 626-6707.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 541-0900. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

November 16-18—**Anesthesiology Update: 1990.** UCD at Monterey Plaza. Fri-Sun. 14 hrs. $350. Contact: UCD.

January 20-26—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Sheraton Hotel, Poipu Beach, Kauai. Sun-Sat. 20 hrs. $345. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

January 25-27—**29th Clinical Conference in Pediatric Anesthesiology.** Children's Hospital Pediatric Anesthesiology Foundation at Stouffer Concourse Hotel. Fri-Sun. 15 hrs. Contact: Katherine Barky, MD, PO Box 54700, Los Angeles 90054.

February 3-8—**Clinical Update in Anesthesiology.** Biennial Western Conference on Anesthesiology at Stouffer's Wailea Beach Resort, Maui, Hawaii. Sun-Fri. Contact: Murray Atnikov, MD, c/o PO Box F110-63, Blaine, WA 98230. (604) 874-5291.

CARDIOLOGY

December 1—**8th Annual Reider Laser Center: International Pulmonary Symposium on Brachytherapy and Argon and ND: YAG Lasers with ND: YAG Laser Workshop.** Memorial/UCI Center for Health Education at Long Beach. Sat. Contact: UCI.

January 24-26—**Cardiology '91.** Cardiovascular Institute at La Jolla Marriott. Thurs-Sat. Contact: Janice Turner, PO Box 2586, La Jolla 92038. (619) 459-1564.

April 22-May 1—**Cardiology for the Consultant: A Physician's Retreat.** Scripps Clinic and Research Foundation at Inn Rancho Santa Fe. 1½ wks. Contact: Mary Ann Morris, 860 SW Scherer Rd, Lee's Summit, MO 64063. (816) 524-5780.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7186.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

(Continued on Page 490)

What we've done for you lately.

We've taken some concrete steps toward making the less exciting parts of your job less of a problem.

Here's what we did.

We developed ways to speed up claims processing and payments. So you can spend more time worrying about patients, and less time worrying about paperwork.

Our new One Call system helps speed up utilization review and preauthorization. So you can get immediate answers to your benefit and eligibility questions with just one call.

And without being transferred or put on hold.

We've also developed a program called Claim Free™, which further expedites the reimbursement process by eliminating paper claims for both you and your Medicare subscribers.

We're continuing to make these changes for one simple reason: The whole point of health care is to take care of people.

And, by taking better care of you, we're doing just that.

Blue Cross of California

We care about what's good for you.

(Continued from Page 488)

DERMATOLOGY

January 17-19—**Workshop in Dermatopathology.** Scripps Clinic and Research Foundation at Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Sat. 20 hrs. $400. Contact: Susan J Buntjer, 400S, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

January 24-26—**Cutaneous Malignancies: 1991 Skin Cancer Update.** Scripps Clinic and Research Foundation at Hyatt Regency, La Jolla. Thurs-Sat. 12 hrs. $350. Contact: Susan Buntjer, 400S, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

EMERGENCY MEDICINE

November 12-16—**Emergency Medicine Symposium III: Pediatrics, OB/GYN, Legal Aspects, Dermatology.** UCSD at Hyatt Regency, La Jolla. Mon-Fri. 32 hrs. $450. Contact: UCSD.

December 10-14—**Emergency Medicine Symposium II: Trauma and Surgery.** UCSD at La Jolla Marriott. Mon-Fri. 32 hrs. $485. Contact: UCSD.

January 14-18—**Emergency Medicine Symposium I: Cardiology, Pulmonary, Neurology.** UCSD at Hyatt Regency, La Jolla. 32 hrs. $485. Contact: UCSD.

February 24-March 1—**Annual Emergency Medicine.** UCD at Hyatt Lake Tahoe, Incline Village, NV. Sun-Fri. 25 hrs. $465. Contact: UCD.

March 18-22—**Symposium II: Trauma and Surgery.** UCSD at La Jolla Marriott. Mon-Fri. 32 hrs. $485. Contact: UCSD.

April 3-6—**Advances in Emergency Medicine.** UCSF at Sheraton Palace Hotel, San Francisco. Wed-Sat. 22 hrs. $435. Contact: UCSF.

FAMILY PRACTICE/PRIMARY CARE

January 26-February 2—**Vascular Update 1991.** University of Washington School of Medicine at Westin Hotel, Kauai, Hawaii. One week. Contact: U/W School of Medicine, Div of CME, SC-50, Seattle 98195. (206) 543-1050.

January 31-February 2—**Adolescent Medicine for the Practitioner.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Sat. Contact: Laurie Jones, Box 400S, Scripps Clinic, 10666 N Torrey Pines Road, La Jolla 92037. (619) 554-9592.

February 11-15—**Family Practice Refresher Course.** UCI at Westin South Coast Plaza, Costa Mesa. Mon-Fri. Contact: UCI.

February 15-18—**43rd Scientific Assembly of the California Academy of Family Physicians.** CAFP at Wyndham Hotel, Palm Springs. Fri-Mon. 23 hrs. Contact: Robert Fagan, (415) 541-0762.

February 20-23—**The Practicing Physician's Approach to the Difficult Headache Patient.** Scripps Clinic and Research Foundation and Diamond Headache Clinic at Wyndham Hotel, Palm Springs. Wed-Sat. 15 hrs. Contact: Idell Applebaum, 5252 N Western Ave, Chicago, IL 60625. (312) 878-5558.

March 15-17—**Psychopharmacology for the Primary Care Physician.** UCSD at Catamaran Resort Hotel, San Diego. Fri-Sun. Contact: Cass Jones, 7916 Convoy Ct, San Diego 92111. (619) 565-9921.

April 6-13—**Primary Care Medicine: Update '91.** UCSF at Waiohai Kauai, Hawaii. 1 week. 20 hrs. $525. Contact: UCSF.

INTERNAL MEDICINE

November 30-December 1—**Northern California Internal Medicine Update.** UCD at Hilton Inn. Fri-Sat. Contact: UCD.

December 6-9—**Fall Symposium on Back Pain.** American Back Society at San Francisco Marriott Hotel. Thurs-Sun. 18 hrs. Contact: Aubrey Swartz, MD, ABS, 2647 E 14th St, Ste 401, Oakland 94601. (415) 536-9929.

January 31-February 2—**Advanced Nephrology: Nephrology for the Consultant.** UCSD at Sheraton Grand Hotel, San Diego. Thurs-Sat. 17 hrs. $350. Contact: Meeting Management, 5665 Oberlin Dr, Ste 110, San Diego 92121. (619) 453-6222.

February 1-3—**8th Annual Reider Laser Symposium-Urology.** Memorial/UCI Center for Health Education at Palm Springs. Fri-Sun. Contact: UCI.

February 3-8—**Winter Urologic Forum.** UCD at Hyatt Regency Lake Tahoe, Incline Village, Nevada. Sun-Fri. 22 hrs. $400. Contact: UCD.

February 15-17—**24th Annual Recent Advances in Neurology.** UCSF at San Francisco. Fri-Sun. 15 hrs. Contact: UCSF.

February 18-20—**Clinical Hematology and Oncology: 1991.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Wed. 18 hrs. $385. Contact: Susan Buntjer, 400S, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

March 6-7—**Advances in Endocrinology and Metabolism.** UCSF at Sheraton Palace Hotel, San Francisco. Wed-Thurs. 14 hrs. $295. Contact: UCSF.

March 8-9—**Diabetes Update.** UCSF at Sheraton Palace Hotel, San Francisco. Fri-Sat. 10 hrs. $245. Contact: UCSF.

OB/GYN

November 12-16—**23rd Review Course in Obstetrics and Gynecology.** USC at Pasadena Hilton Hotel. Mon-Fri. $640. 38 hrs. Contact: USC.

November 29-December 1—**Nebraska OB/GYN Society Meeting.** Nebraska OB/GYN at Las Vegas, Nevada. Thurs-Sat. Contact: University of Nebraska Medical Center, 42nd and Dewey Ave, Omaha, NE 68105-1065. (402) 559-4152.

February 1-3—**8th Annual Reider Laser Symposium-Gynecology.** Memorial/UCI Center for Health Education at Palm Springs. Fri-Sun. Contact: UCI.

February 14-17—**46th Annual Postgraduate Assembly.** OB-GYN Assembly of Southern California at Beverly Hilton Hotel, Beverly Hills. Thurs-Sun. 28 hrs. Contact: OB-GYN Assembly, 5820 Wilshire Blvd, No. 500, Los Angeles 90036. (213) 937-5514.

April 10-14—**Pacific Coast Fertility Society Annual Scientific Program.** Pacific Coast Fertility Society at Stouffer Esmeralda Resort, Indians Wells. Wed-Sun. 22 hrs. Contact: Director of Medical Education, 5820 Wilshire Blvd, No 500, Los Angeles 90036. (213) 937-5514.

OCCUPATIONAL AND ENVIRONMENTAL MEDICINE

January 28-February 8—**Occupational and Environmental Medicine: Session I.** UCSF at Cathedral Hill Hotel, San Francisco. 1½ weeks. 80 hrs. $1,200. Contact: UCSF.

February 11-15—**Occupational and Environmental Medicine: Session III.** UCSF at Cathedral Hill Hotel, San Francisco. Mon-Fri. 40 hrs. $600. Contact: UCSF.

March 13-17—**Mountain Medicine: '91.** American College of Emergency Physicians at Squaw Valley. Wed-Sun. 22 hrs. $395. Contact: Howard Donner, MD, PO Box 321, Yreka 96097. (800) 888-5632.

OPHTHALMOLOGY

November 30-December 2—**American Academy of Ophthalmology Regional Update Course.** American Academy of Ophthalmology at Los Angeles. Fri-Sun. Contact: Gary Holland, (213) 825-9508.

December 13-14—**New Ideas on Common Retinal Disorders.** UCSF at Grand Hyatt Union Square, San Francisco. Thurs-Fri. 12 hrs. $300. Contact: UCSF.

January 13-16—**Contact Lens Association of Ophthalmologists 1991 Annual Meeting.** CLAO at Caesars Palace, Las Vegas, Nevada. Sun-Wed. Contact: CLAO, 523 Decatur St, Ste One, New Orleans, LA 70130-1027. (504) 581-4000.

February 3-7—**10th Annual Squaw Valley Retina Symposium.** Alta-California Ophthalmological Society at Squaw Valley Inn, Olympic Valley. Sun-Thurs. 16 hrs. Contact: Mercy General Hospital, Community Relations, 4001 "J" St, Sacramento 95819. (916) 454-4410.

February 8-10—**60th Midwinter Clinical Conference.** Research Study Club of Los Angeles at Moseley/Salvatori Conference Center, Los Angeles. Fri-Sun. Contact: Research Study Club, PO Box 1216, Murrieta 92362. (714) 677-4482.

ORTHOPEDICS

December 6—**Common Musculoskeletal Problems—Foot and Ankle.** VA Medical Center Sepulveda. Thurs. 5 hrs. Contact: Arun Mehta, MD, Rehabilitation Medicine Service (117), VAMC Sepulveda 91343. (818) 895-9344.

(Continued on Page 492)

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OTOLARYNGOLOGY

February 8-10—**60th Midwinter Clinical Conference.** Research Study Club of Los Angeles at Moseley/Salvatori Conference Center. Fri-Sun. Contact: Research Study Club, PO Box 1216, Murrieta 92362. (714) 677-4482.

January 18-20—**Triological Society Western Section.** Triological Society at Santa Barbara Biltmore Hotel. Fri-Sun. Contact: David Hilding, MD, Ste 1, Hospital Dr, Price, UT 84501. (801) 637-4327.

PATHOLOGY

February 13-15—**Clinical Laboratory Molecular Analysis.** Scripps Clinic and Research Foundation at Hyatt Regency Hotel, La Jolla. Wed-Fri. 21 hrs. $375. Contact: Laurie Jones, Box 400S, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-9592.

April 17-19—**12th Annual Advances in Infectious Diseases.** UCSF at Sheraton Palace Hotel, San Francisco. Wed-Fri. 18 hrs. $395. Contact: UCSF.

PEDIATRICS

December 1—**8th Annual Binational Pediatric Conference.** Children's Hospital San Diego at Mercy Hospital Education Center, San Diego. Sat. 5 hrs. Contact: CME Dept, Children's Hospital, (619) 576-4072.

December 8-9-**Stabilization and Management of the Critically Ill Child.** UCSF at Hyatt Regency Hotel, San Francisco. Sat-Sun. 9 hrs. Contact: UCSF.

January 23-26—**Health Science Response to Child Maltreatment 1991.** Children's Hospital San Diego at U S Grant Hotel, San Diego. Wed-Sat. 22 hrs. Contact: Children's Hospital, (619) 576-5814.

February 8-10—**Current Concepts in Pediatric Medicine 1991.** Children's Hospital San Diego at Hyatt Islandia Hotel, San Diego. Fri-Sun. 18 hrs. Contact: CME Dept. Children's Hospital, (619) 576-4072.

PSYCHIATRY

November 12-16—**Introduction to Medical Hypnosis.** UCSD at Inn at Del Mar. Mon-Fri. Contact: UCSD.

January 27-February 1—**17th Annual Midwinter Program for Psychiatrists: Special Focus on Psychic Trauma.** UCD at Hyatt Regency, Incline Village, Nevada. Sun-Fri. 25 hrs. $395. Contact: UCD.

February 28-March 1—**The Dimensions of Caring 1991: A Symposium on Palliative Care of the Cancer Patient.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Fri. Contact: Laurie Jones, Box 400S, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-9592.

RADIOLOGY

December 7-9—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton Resort Hotel, Laguna Niguel. Fri-Sun. 18 hrs. $400. Contact: UCSD.

January 13-18—**Neuro and Musculoskeletal MR Applications.** UCSF at Hyatt Regency, Kauai, Hawaii. Sun-Fri. 24 hrs. $595. Contact: UCSF.

January 19-21—**Advanced Seminars in Diagnostic Imaging.** UCSF at Ritz-Carlton Resort Hotel, Laguna Niguel. Sat-Mon. 20 hrs. $400. Contact: UCSF.

February 1-3—**43rd Midwinter Radiological Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Fri-Sun. 17 hrs. $395. Contact: LARS, PO Box 91215, Los Angeles 90009-1215. (213) 827-9078.

February 4-5—**Angio-Interventional Radiology.** UCSD at Le Meridien Hotel, San Diego. Mon-Tues. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

Feburary 4-8—**Magnetic Resonance Imaging in the Desert.** UCSF at Ritz-Carlton, Rancho Mirage. Mon-Fri. 22 hrs. $595. Contact: UCSF.

February 5-9—**17th Annual Mid-Pacific Radiological Conference.** Los Angeles Radiological Society at Maui Marriott Hotel, Maui, Hawaii. Tues-Sat. 16 hrs. $395. Contact: LARS, PO Box 91215, Los Angeles 90009. (213) 827-9078.

February 6—**Intraluminal Ultrasound.** UCSD at Le Meridien Hotel, San Diego. Wed. 6 hrs. $150. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 6-9—**Introduction to Doppler Principles.** UCSD at Le Meridien Hotel, San Diego. Wed-Sat. 7 hrs. $150. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 6-9—**Duplex Imaging.** UCSD at Le Meridien Hotel, San Diego. Wed-Sat. 22 hrs. $495. Contact: UCSD.

February 9-10—**Obstetric and Gynecology Sonographic Update: Focus on CNS Abnormalities.** UCSD at Le Meridien Hotel, San Diego. Sat-Sun. 10 hrs. $150. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 11-15—**Contemporary Diagnostic Imaging Featuring MRI, CT, US and Interventional Radiology.** Stanford University at Ritz-Carlton Hotel, Mauna Lani, Hawaii. Mon-Fri. 20 hrs. $515. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 1-3—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton Resort Hotel, Laguna Niguel. Fri-Sun. 18 hrs. $400. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 4-8—**Magnetic Resonance Imaging.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 27 hrs. $500. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 16-18—**Breast Imaging Update.** UCSF at Fairmont Hotel, San Francisco. Sat-Mon. 16 hrs. $350. Contact: UCSF.

April 7-12—**Diagnostic Imaging: 1991.** UCSF at Ritz-Carlton Mauna Lani, Kona, Hawaii. Sun-Fri. 23 hrs. $595. Contact: UCSF.

April 21-26—**11th Annual San Diego Resident's Radiology Review Course.** UCSD at Hyatt Regency Hotel, La Jolla. Sun-Fri. 39 hrs. $435. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

April 27—**Introduction to Interventional Radiology.** UCSD at Hyatt Regency Hotel, La Jolla. Sat. 8 hrs. $100. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

REHABILITATIVE/THERAPEUTIC

December 10-11—**Clinical Care of the AIDS Patient.** UCSF at Hyatt Regency Embarcadero, San Francisco. Mon-Tues. 13 hrs. $250. Contact: UCSF.

January 23-26—**6th International Symposium on Platinum and Other Metal Coordination Compounds in Cancer Chemotherapy.** UCSD at Sheraton Harbor Island East Hotel, San Diego. Wed-Sat. Contact: Cass Jones, 7916 Convoy Ct, San Diego 92111. (619) 565-9921.

February 7-9—**Biotherapy of Cancer: A Symposium for Clinicians and Nurses.** Hoag Hospital at Newport Beach Marriott. Thurs-Sat. 15 hrs. $375. Contact: Nomi Feldman, 5665 Oberlin Dr, Ste 110, San Diego 92121. (619) 453-6222.

February 18-20—**11th Betty Ford Center Conference on Chemical Dependency.** Annenberg Center for Health Science. Mon-Wed. Contact: ACHSE, 39000 Bob Hope Dr, Rancho Mirage 92270. (800) 321-3690.

SURGERY

November 1990-December 1990—**Temporal Bone Surgical Dissection Courses: 1990.** House Ear Institute, 5 days per month. 53 hrs. $975. Contact: Antonio de la Cruz, MD, Director of Education, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

November 12-16—**Hyperbaric Medicine.** UCI/Memorial Medical Center at Long Beach. Mon-Fri. 30 hrs. $650. Contact: Celia Loney, 2801 Atlantic Ave, PO Box 1428, Long Beach 90801. (213) 595-2000.

November 17—**C02 Surgical Laser Workshop.** Scripps Clinic and Research Foundation. Sat. 8 hrs. $600. Contact: Susan Buntjer, Box 400S, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

January 18-19-**What's New in General Surgery: 13th Annual Postgraduate Course.** UCD at Capitol Plaza Holiday Inn, Sacramento. Fri-Sat. Contact: UCD.

MULTIPLE TOPICS

November 18-21—**Putting Prevention into Practice.** SDSU at Hyatt Islandia Hotel, San Diego. Sun-Wed. 23 hrs. $140. Contact: Mickey Pagan, (619) 594-5904.

March 7-9—**Recent Advances in Geriatric Medicine: New Treatment Options for Old Problems.** UCSD at Pan Pacific Hotel, San Diego. Thurs-Sat. Contact: Cass Jones, 7916 Convoy Ct, San Diego 92111. (619) 565-9921.

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(Continued from Page 492)

April 25-28—**Nevada State Medical Association Annual Meeting.** NSMA at Quail Lodge, Carmel. Thurs-Sun. Contact: Nevada State Medical Association, 3660 Baker Ln, Reno, NV 89502. (702) 825-6788.

February 20-23—**The Practicing Physician's Approach to the Difficult Headache Patient.** Scripps Clinic and Diamond Headache Clinic at Wyndham Hotel, Palm Springs. Wed-Sat. 15 hrs. Contact: Idell Applebaum, 5252 N Western Ave, Chicago, IL 60625. (312) 878-5558.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

November 15—**Colorado Radiological Society.** Hyatt Regency DTC, Denver. Thurs. Contact: Carol Goddard, (303) 770-6048.

December 3-7—**Respiratory Therapy Traineeship.** The Children's Hospital, Denver. Mon-Fri. Contact: Jeff Griebel, (303) 861-6227.

January—**Perinatal Continuing Education Program.** The Children's Hospital, Denver Community Hospital-based, 40-week, self-study program for all perinatal healthcare providers. Contact: Pat Winter, (303) 861-6668.

January 17—**Colorado Radiological Society.** Hyatt Regency DTC, Denver. Thurs. Contact: Carol Goddard, (303) 770-6048.

January 26-31—**Uvetitis and Pathology.** Colorado Ophthalmological Society at Westin Hotel, Vail. Sat-Thurs. Contact: Carol Goddard, (303) 770-6048.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver, CO. (303) 270-5195.

IDAHO

February 27-March 2—**Sun Valley Program.** Pierce County Medical Society (Washington) College of Medical Education at Sun Valley. Wed-Sat. Contact: PCMS CME, 705 S 9th, No. 203, Tacoma, WA 98405. (206) 627-7137.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

November 17—**Anxiety Disorders.** University of New Mexico School of Nursing and Pharmacy Auditorium, Albuquerque. Sat. Contact: Psychiatric Medical Association, PO Box 26666, Albuquerque 87125. (505) 291-5375.

November 30-December 1—**Trauma Update '90.** Clarion Four Seasons, Albuquerque. Fri-Sat. Contact: University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

December 6-8—**American College of Physicians New Mexico Scientific Meeting.** Hyatt Regency, Albuquerque. Thurs-Sat. Contact: University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

January 19—**Personality Disorders.** University of New Mexico School of Nursing and Pharmacy Auditorium, Albuquerque. Sat. Contact: Marsha VerPloegh, Psychiatric Medical Association, PO Box 26666, Albuquerque 87125. (505) 291-5375.

March 16—**AIDS Update.** University of New Mexico School of Nursing and Pharmacy Auditorium, Albuquerque. Sat. Contact: Marsha VerPloegh, Psychiatric Medical Association, PO Box 26666, Albuquerque 87125. (505) 291-5375.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

November 16-17—**Pediatric Update** (Sponsor: UUMC). Fri-Sat. Holiday Inn, St George. Contact: (801) 581-8664.

December 7-9—**Laser Surgery—Laparoscopic Cholecystectomy** (Sponsor: UUMC). Fri-Sun. The Laser Institute, University of Utah, Salt Lake City. Contact: J. Freedman, (801) 581-7001.

January 1-6—**Arthritic Hip, Knee & Shoulder** (Sponsor: UUMC). Mon-Fri. Snowbird. Contact: (801) 581-8664.

January 15-19—**Arthroscopic Surgery 1991** (Sponsor: UUMC). Tues-Sat. Phoenix, Arizona. Contact: (801) 581-7602.

January 17-21—**Ethics and Health** (Sponsor: UUMC). Thurs-Mon. University of Utah, Olpin Union Building, Salt Lake City. Contact: (801) 581-8664.

January 25-27—**Laser Surgery—Laparoscopic Cholecystectomy** (Sponsor: UUMC). Fri-Sun. The Laser Institute, University of Utah, Salt Lake City. Contact: J. Freedman, (801) 581-7001.

February 1-3—**Pediatric Update** (Sponsor: UUMC). Fri-Sun. Jackson, Wyoming. Contact: (801) 581-7001.

(Continued on Page 496)

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Warnings: CECLOR SHOULD BE ADMINISTERED CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. PENICILLINS AND CEPHALOSPORINS SHOW PARTIAL CROSS-ALLERGENICITY. POSSIBLE REACTIONS INCLUDE ANAPHYLAXIS.

Administer cautiously to allergic patients.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics. It must be considered in differential diagnosis of antibiotic-associated diarrhea. Colon flora is altered by broad-spectrum antibiotic treatment, possibly resulting in antibiotic-associated colitis.

Precautions:
• Discontinue Ceclor in the event of allergic reactions to it.
• Prolonged use may result in overgrowth of nonsusceptible organisms.
• Positive direct Coombs' tests have been reported during treatment with cephalosporins.
• Ceclor should be administered with caution in the presence of markedly impaired renal function. Although dosage adjustments in moderate to severe renal impairment are usually not required, careful clinical observation and laboratory studies should be made.
• Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.
• Safety and effectiveness have not been determined in pregnancy, lactation, and infants less than one month old. Ceclor penetrates mother's milk. Exercise caution in prescribing for these patients.

Adverse Reactions: (percentage of patients)

Therapy-related adverse reactions are uncommon. Those reported include:
• Hypersensitivity reactions have been reported in about 1.5% of patients and include morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs' tests each occur in less than 1 in 200 patients. Cases of **serum-sickness-like** reactions have been reported with the use of Ceclor. These are characterized by findings of erythema multiforme, rashes, and other skin manifestations accompanied by arthritis/arthralgia, with or without fever, and differ from classic serum sickness in that there is infrequently associated lymphadenopathy and proteinuria, no circulating immune complexes, and no evidence to date of sequelae of the reaction. While further investigation is ongoing, **serum-sickness-like** reactions appear to be due to hypersensitivity and more often occur during or following a second (or subsequent) course of therapy with Ceclor. Such reactions have been reported more frequently in children than in adults with an overall occurrence ranging from 1 in 200 (0.5%) in one focused trial to 2 in 8,346 (0.024%) in overall clinical trials (with an incidence in children in clinical trials of 0.055%) to 1 in 38,000 (0.003%) in spontaneous event reports. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy; occasionally these reactions have resulted in hospitalization, usually of short duration (median hospitalization = two to three days, based on postmarketing surveillance studies). In those requiring hospitalization, the symptoms have ranged from mild to severe at the time of admission with more of the severe reactions occurring in children. Antihistamines and glucocorticoids appear to enhance resolution of the signs and symptoms. No serious sequelae have been reported.
• Stevens-Johnson syndrome, toxic epidermal necrolysis, and anaphylaxis have been reported rarely. Anaphylaxis may be more common in patients with a history of penicillin allergy.
• Gastrointestinal (mostly diarrhea): 2.5%
• Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment.
• As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.
• Rarely, reversible hyperactivity, nervousness, insomnia, confusion, hypertonia, dizziness, and somnolence have been reported.
• Other: eosinophilia, 2%; genital pruritus or vaginitis, less than 1% and, rarely, thrombocytopenia and reversible interstitial nephritis.

Abnormalities in laboratory results of uncertain etiology
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(Continued from Page 494)

February 4-8—**Surgical Pathology** (Sponsor: UUMC). Mon-Fri. Park City. Contact: K. Rassmussen, (801) 379-7178.

February 10-15—**Interventional Radiology** (Sponsor: UUMC). Sun-Fri. Park City. Contact: Judy Gallegos, (801) 581-8188.

February 10-15—**Update in Clinical Microbiology and Immunology** (Sponsor: UUMC). Sun-Fri. Park City. Contact: Midge Beckman, (801) 581-7480.

February 11-16—**Microsurgery Workshop** (Sponsor: UUMC). Mon-Sat. University Park Hotel, Salt Lake City. Contact: (801) 581-8664.

February 11-16—**Orbital & Craniofacial Surgery** (Sponsor: UUMC). Mon-Sat. Snowbird. Contact: (801) 581-8664.

February 11-17—**Family Practice Refresher Course** (Sponsor: UUMC). Mon-Sun. Salt Lake Hilton, Salt Lake City. Contact: K. Chisholm, (801) 581-7234.

February 15-19—**The 35th Anesthesiology Update** (Sponsor: UUMC). Fri-Tues. Snowbird. Contact: V. Larsen, (801) 581-6393.

February 17-20—**The 32nd Annual Ob/Gyn Update** (Sponsor: UUMC). Sun-Wed. The Yarrow, Park City. Contact: S. Martin, (801) 581-5501.

February 19-23—**Pediatric Emergency Medicine** (Sponsor: UUMC). Wed-Sun. The Marriott Hotel, Salt Lake City. Contact: (801) 588-2000.

SPONSORS OF COURSES—ABBREVIATIONS

AHA: American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.

BYUHS: Brigham Young University Health Services, McDonald Student Health Center, Brigham Young University, Provo 84602. (801) 378-2771.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 S 300 East, Salt Lake City 84101. (801) 262-3461.

DMC: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 673-9681.

HCH: Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

144: 144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave, Salt Lake City 84103. (801) 363-1221.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

SMH: St Mark's Hospital, 1200 E 3900 South, Salt Lake City 84117. (801) 268-7111.

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USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

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Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

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December 13-15—**6th Annual ID Conference.** Everett. Thurs-Sat. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

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January 23—**Pesticide Medicine.** Seattle. Wed. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

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March 1-2—**Psychiatric and Psychological Issues in Medical Practice.** Seattle. Fri-Sat. Contact: VMMC.

March 13-15—**Spirometry Training for Worker Screening.** Seattle. Wed-Fri. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

March 14-15—**Tacoma Academy of Internal Medicine.** Tacoma. Thurs-Fri. Contact: PCMS CME.

March 15—**Inflammatory Bowel Disease.** Seattle. Fri. Contact: VMMC.

March 22-23—**Ophthalmology (WSAO)—Annual President's Meeting.** Seattle. Fri-Sat. Contact: (206) 441-9762.

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April 12-13—**Surgical Club.** Tacoma. Fri-Sat. Contact: PCMS CME.

April 12-13—**Low-Back Pain.** Seattle. Fri-Sat. Contact: VMMC.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 496)

April 13-14—**Benton-Franklin County Medical Society Annual Meeting.** Tri-Cities. Sat-Sun. Contact: (509) 783-8616.

April 15-18—**The Best Approach 1991: Effective, Efficient Strategies in Cardiology, Orthopedics, Gastroenterology, and Pediatrics.** Kauai Sheraton, Hawaii. Fri-Mon. Contact: Group Health, (206) 326-3441.

April 15-26—**PM & R Review.** Seattle. Fri-Tues. Contact: U/W.

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COURSE SPONSORS AND CONTACT INFORMATION

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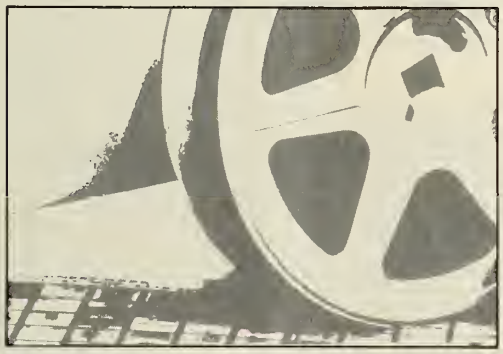

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Biomedical Science

Molecular Analysis of the Pathogenesis of β-Cell Destruction in Insulin-Dependent Diabetes Mellitus

ÅKE LERNMARK, PhD; HEIKE BÄRMEIER, MD, PhD; SYAMALIMA DUBE, PhD; WILLIAM HAGOPIAN, MD, PhD; ALLAN E. KARLSEN, PhD; HELLE MARKHOLST, MD; CINDY WILSON; *and* RALF WASSMUTH, MD, PhD, *Seattle, Washington*

Presented at the Plenary Session, Western Association of Physicians, Carmel, California, February 6, 1990.

(Lernmark Å, Bärmeier H, Dube S, et al: Molecular analysis of the pathogenesis of β-cell destruction in insulin-dependent diabetes mellitus. West J Med 1990 Nov; 153:499-502)

The epidemiology of insulin-dependent diabetes mellitus (IDDM) suggests that this disease may develop at any age.[1,2] The life-time risk for IDDM is becoming more clear based on the results of large population studies, primarily in northern Europe and in England. In a population of 10 million inhabitants, about 100,000 children will be born per year. Of those 100,000 newborns, 1,000 will have IDDM develop within their lifetime. The age distribution at onset is such that the disease will develop in 40% of them before they reach age 15 years, 30% at between 15 and 34 years of age, and in the remaining 30% up until old age.

What are the different factors that play a role in the development of IDDM? The disease is associated with a specific loss of the pancreatic β cells.[3] An autoimmune reaction is implicated in IDDM. The mechanisms by which the immune system is able to recognize the β cell as the specific target are not known. The molecular genetics of this disease suggest that there are susceptibility genes which are closely associated with HLA.[4-6] Recent studies indicate that the HLA-DQ locus on chromosome 6 is closer to diabetes than any previous HLA markers (Table 1). The problem when studying IDDM is that this particular part of chromosome 6 consists of genes that tend to be inherited together.[4,6] There is a low frequency of crossing over that creates linkage disequilibrium. The closer a marker is to the putative susceptibility gene sequence, the larger the population study needed to define the locus through occasional crossing-over events. Alternatively, IDDM needs to be studied in a genetic background that is different from whites—that is, in Japanese or in African Americans in whom classical IDDM develops. On chromosome 6 the HLA association was first observed at the B locus, with the specificities B8 and B15. It was then evident that there was a linkage disequilibrium with DR. DR3 and DR4 were the markers that were found to be more closely related to IDDM. Molecular cloning analysis now suggests that HLA-DQ is closer to diabetes mellitus than the previous two because of linkage disequilibrium.

There are several major "players" in the autoimmune reaction toward the pancreatic β cells (Table 2). One cell is the antigen-presenting cell, the macrophage. The macrophage is assumed to present antigen to the T-helper cell. The specific T-helper cell and its receptor are yet to be defined. This is difficult largely because the structure of the major known β-cell autoantigen, the molecular weight (M_r) 64,000 protein, is not known.[1,3] Patients with IDDM have a high frequency of M_r 64,000 antibodies at the time the disease starts. Another antigen, insulin, is fully characterized. The frequency of insulin autoantibodies in patients with IDDM is, however, only 50%, which renders the possibility questionable that insulin is the putative autoantigen to cause the disease.

The antigen-presenting cells express class II molecules. The class II molecules bind a part of an autoantigen that may be the initiating factor for IDDM. Molecular cloning and x-ray crystallography have made it possible to produce a model of class II antigens (Figure 1).[7] It has been suggested by comparing the amino acid sequences of class II antigens that the position 57 amino acid may be implicated in a resistance or susceptibility to IDDM.[6] It appears, however, that the position 57 is likely to be yet another example of linkage disequilibrium to the putative insulin-dependent diabetes susceptibility genes (Table 3).[4] In the first study that was carried out in multiplex families in Pittsburgh, Pennsylvania, none of the patients were homozygous for aspartate at position 57. The relative risk was high, allowing the authors to speculate that this particular amino acid is the putative susceptibility gene. Studies in Norway, however, indicated that 2% of the patients in Norway are homozygous for Asp and diabetes still developed. In Poland, 9% are Asp-Asp-positive; in China the frequency of Asp-Asp-positive patients increases to 22%; and in Japan 56% of the patients are Asp-Asp-positive. These patients have DQ types other than those found among the northern Europeans.

By using restriction fragment length polymorphism studies, it is possible to further analyze the restriction fragment polymorphism to generate new fragments associated with IDDM.[8] In one particular restriction fragment polymorphism analysis, diabetic patients have a 12-kilobase (kb) fragment or a 4-kb fragment. Shown in Table 4 are IDDM children analyzed for HLA-B, -DR, and -DQ, and for restriction fragment length polymorphism. The same 11 patients were DR3/4, but additional patients were DR3/4 and had other B8 or B15 specificities on their chromosomes. Proceeding along chromosome 6 will therefore result in an increase in the number of these putative markers that come closer to the "diabetes gene" by statistical analysis of association. The 12-kb fragment has, for example, been found in all the Japanese IDDM patients studied so far.[9]

What is the cellular immunity in insulin-dependent diabetes? In humans we know little despite the fact that insulitis was first described 90 years ago.[10,11] The presence of

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ABBREVIATIONS USED IN TEXT

IDDM = insulin-dependent diabetes mellitus
M_r = molecular weight
NIDDM = non-insulin-dependent diabetes mellitus

macrophages and T and B cells has been documented in a few patients whose pancreases were available for study when the disease began. In the peripheral blood there is little to be found; most often reported is a transient decrease in the T-cell suppressor cells.[12,13] In BB rats and NOD mice, the evidence is more substantial. Insulin-dependent diabetes may be transferred by T cells, and in NOD mice spectacular progress has been made to transfer the disease with cloned CD4-positive cells.[14,15] CD8-positive T cells have also been cloned and shown to protect from the development of insulitis, preventing an accelerated onset of diabetes. An important aspect of IDDM is that macrophages infiltrate the islet.[16] Macrophages are known to elaborate factors such as interleukin 1. In vitro and in vivo in BB rats, interleukin 1 is an effective modulator of the β-cell function and of IDDM, respectively (Figure 2).[17-19] The usual onset curve in diabetes-prone BB rats shows that IDDM develops around day 80 to 90. Daily injections of a high dose of interleukin 1 stimulate the occurrence of diabetes. Low doses of interleukin 1 prevent the disease and decrease the frequency of diabetes mellitus not only in BB rats but also in NOD mice.[20] The question is, are these cytokines modulating both the β cells and the immune response? What are the effects of other cytokines, alone or in combination? Experiments to answer these questions are a major focus in autoimmune as well as in autoimmune diabetes research. Clinical trials are to be expected, perhaps not with interleukin 1 but with interleukin-1 binding proteins or interleukin-1 receptors in attempts to inhibit an ongoing autoimmune destruction of the β cells.

What are the markers that indicate diabetes will develop? Islet cell antibodies are one marker, and insulin autoantibodies are another. Both antibody markers have been standardized internationally, and quantitative assays are available.[21,22] The prevalence of islet cell antibodies and in-

TABLE 1.—*HLA-DR and -DQ Studies in Swedish Patients With Insulin-Dependent Diabetes Mellitus (IDDM) and Controls Suggest That the DQ Locus Is the Major Susceptibility Locus**

Allele	*IDDM, n = 68*	*Controls, n = 86*	*Odds Ratio*
DR3	38	14	6.5
DQw2	42	20	5.3
DR4	58	39	7
DQw8	58	34	8.9
DR 3/4	30	7	8.9
DQw2/w8	34	4	20.5

*From Wassmuth and Lernmark.[4]

TABLE 2.—*The Loss of β Cells Due to Abnormalities in the Immune Response Pathway*

Immune Response Pathway	*Cells Involved*
Antigen	Islet β cells (64,000-dalton protein, insulin, or other antigens)
Antigen presentation	Macrophages; dendritic cells
T-cell recognition	T-helper cells; cytotoxic T cells
Autoantibody formation	B lymphocytes

TABLE 3.—*HLA-DQ Asp-57 Allele in Insulin-Dependent Diabetes Mellitus in Different Ethnic Groups**

		% Positive		
Country of Origin	*Cohort*	*Asp/Asp*	*Non-Asp/Asp*	*Non-Asp/Non-Asp*
United States†	P	0	4	96
	C	34	46	20
Norway	P	2	15	83
	C	22	51	27
Poland	P	9	38	52
	C	10	31	43
China	P	22	72	6
	C	95	5	0
Japan	P	56	44	0
	C	95	5	0

C = relatives, P = patients

*From Wassmuth and Lernmark.[4]
†Pittsburgh, Pennsylvania, in which studies were carried out in multiplex families.

TABLE 4.—*HLA Specificities and DQ Polymorphisms in Linkage Disequilibrium**

	Patients,	
HLA Specificity†	*No.*	*(%)*
B8	29	(46)
B15	29	(46)
B8/B15	11	(18)
DR3	36	(56)
DR4	55	(87)
DR3/4	29	(46)
DQw2	41	(65)
DQw8	55	(87)
DQw2/8	34	(54)
IVS-1, 4 kb	44	(70)
IVS-1, 12 kb	55	(87)
IVS-1, 4 kb/12 kb	37	(59)

*From Michelsen et al[8] and unpublished data (R. Wassmuth, J. Ludvigsson, and Å. Lernmark, 1990). A total of 63 children with insulin-dependent diabetes mellitus, aged 0 to 15 years at the clinical onset, from Johnny Ludvigsson, MD, Linköping, Sweden, were investigated.
†IVS-1 refers to a genomic DNA probe that is isolated from the HLA-DQ β-chain gene and represents part of the first intervening sequence.

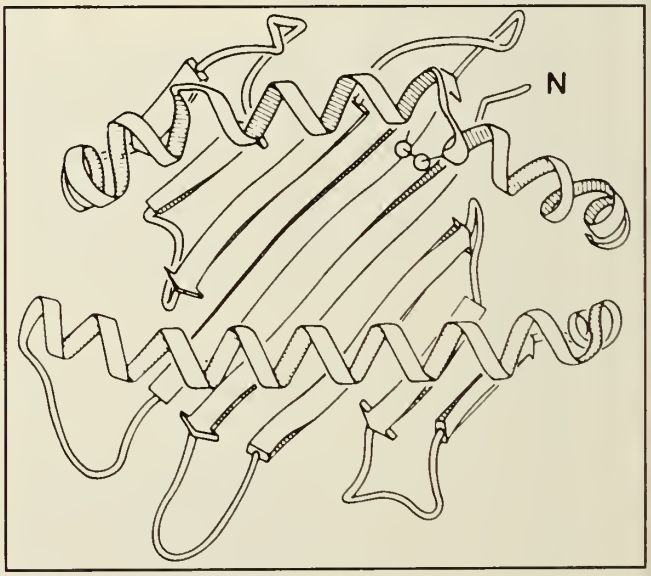

Figure 1.—The hypothetical structure of the antigen-binding cleft of the HLA class II molecule is shown (from Bjorkman et al,[7] reprinted with permission from *Nature*, copyright 1987, Macmillan Magazines Ltd).

sulin autoantibodies at onset is between 60% and 90% and 30% and 40%, respectively.[1,3] The prevalence of islet cell antibodies decreases with increasing age when diabetes begins. In patients with IDDM with an older age at onset, the frequency of islet cell antibodies is lower at the time diabetes starts. In first-degree relatives, the frequency of islet cell antibodies may be higher than the frequency of IDDM, and some of these persons may have subclinical IDDM. It should be noted, however, that only 10% of patients with newly occurring disease have a first-degree relative with IDDM.[1,2] Other persons at risk may be patients with other autoimmune diseases, such as thyroiditis,[1] or patients with non-insulin-dependent diabetes mellitus (NIDDM).[23] Recent studies in Sweden and Finland indicate, however, that the frequency of islet cell antibodies (3% to 4%) in the background population is about ten times higher than the prevalence (0.15% to 0.2%) of the disease.[1] Islet cell antibodies, therefore, are not a powerful marker for IDDM in the background population. For example, in our study, nine children of the healthy group of matched controls had islet cell antibodies.[24] Diabetes developed in two of them during a three-year follow-up, and the other seven children lost their islet cell antibodies. The predictive value for an islet cell antibody test to find diabetes in patients 15 years of age or younger is only 5%. The sensitivity of the test is 81% and the specificity 98%. This predictive value was much different from that of a group of NIDDM patients who were found to be positive for islet cell antibodies at the time of clinical diagnosis.[23] The sensitivity for this group of patients who later became insulin-dependent was 72% and the specificity 96%. The predictive value for insulin dependency to develop in a patient with NIDDM with islet cell antibodies was 84%.[23] This group of patients represents roughly 10% of those with NIDDM at clinical onset and may be important in future immune intervention studies to prevent insulin dependency.

Further problems in understanding insulin-dependent diabetes have become evident in a recent study of first-degree relatives.[25] Using a β-cell function test, all of the relatives were at the normal level or below, but despite the presence of islet cell antibodies or insulin autoantibodies, diabetes did not develop during a follow-up of one to four years. A group of persons positive for islet cell antibodies showed that some of them maintained their level of β-cell function. Other persons lost their islet cell antibodies, and although a decline occurred in some persons, diabetes is yet to develop. Taken together, also in first-degree relatives, islet cell antibodies and insulin autoantibodies are insufficient to predict the occurrence of the disease. Physicians must make attempts to understand what other mechanisms are involved in the progression to clinical disease and realize that subclinical insulitis or IDDM, or both, in association with autoantibodies may be more common than heretofore acknowledged.

Is there another such test already available? By immune precipitation of serum with radioactively labeled human, rat, or dog islets, there is an autoantigen of M_r 64,000 that is present among 70% to 80% of patients with newly occurring IDDM.[1,3] Our preliminary data indicate that the presence of M_r 64,000 antibodies among first-degree relatives is associated with a continuous loss of β-cell function irrespective of insulin autoantibodies or islet cell antibodies.[26] Further experiments will be needed to elucidate this observation.

In summary, IDDM develops in genetically susceptible persons. We speculate that HLA-DQ controls the development of tolerance to cell antigens. Is there a hole for the M_r 64,000 protein in the lymphocyte repertoire? Access to this protein will make it possible to generate T cells to understand the role of the T-cell receptor in the development of the disease and devise or design treatment modalities that can be used to interfere with this process.

Finally, environmental factors such as viruses, including mumps, Coxsackie, and rubella viruses, are all implicated in the pathogenesis of IDDM. Genetic factors provide susceptibility because certain HLA-DR or -DQ types are necessary but not sufficient. Environmental insults may potentiate an immune-mediated β-cell destruction that may already be initiated at birth. It is hoped that further experiments will disclose ways by which we can better predict the occurrence of IDDM and design new treatment strategies to prevent the clinical onset of this disorder.

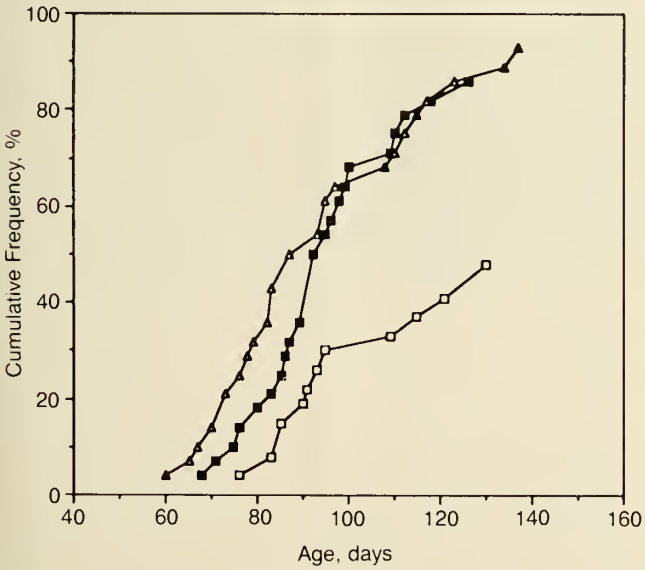

Figure 2.—Effects are shown of injecting interleukin-1β every other day to diabetes-prone BB rats in a high dose (△) to induce an earlier onset and in a low dose (□) to prevent the occurrence of the disease. Control BB rats were injected with a saline solution (■) every other day (from Wilson et al[19]).

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Articles

Sources of Supply of Selected Immunobiologics, 1990

S. BENSON WERNER, MD, MPH, *Berkeley, California*

Information on the availability and sources of new or infrequently used immunobiologics can be hard to obtain. Private practitioners and public health departments in California (and elsewhere in the Western states) occasionally call the Disease Control Section of the California Department of Health Services in their search for these immunobiologics. Information about rarely used biologics was last published in the November 1982 issue of THE WESTERN JOURNAL OF MEDICINE.* There have been so many changes since then that an update is in order.

While not all producers of the materials listed have been identified, an exhaustive effort was made before stating that an immunobiologic material is "not available." Any corrections or additions, however, that are now known, or become known, would be appreciated so that the list can be kept up-to-date.

The California Department of Health Services in no way endorses the products or manufacturers that are mentioned, nor does it necessarily recommend that any of these products be used. Staff members of the California Disease Control Section remain available for consultation on these biologics and their use ([415] 540-2566).

Skin Test Antigens

Actinomycosis

Not available.

Atypical Mycobacteria

Not available in the United States, but antigens are under evaluation by the Centers for Disease Control.

- Available in England from Public Health Laboratory Service, Mycobacterium Reference Unit, University Hospital of Wales, Health Park, Cardiff CF4 4XW, Great Britain, telephone 0222-755944, extension 2049, telecopier (FAX) 0222-751729.
- Available in Denmark as unlicensed skin test preparations (sensitins) prepared from *Mycobacterium avium, Mycobacterium chelonei, Mycobacterium fortuitum, Mycobacterium intracellulare, Mycobacterium marinum, Mycobacterium scrofulaceum,* and other *Mycobacterium* species by special arrangement with M. Magnusson, Tuberculin Department, Statens Seruminstitut, Artillerivej 5, DK-2300, Copenhagen S, Denmark, telephone 45-31-952817, Telex 31316 Serum DK, FAX 45-31-955822.

Blastomycin (Blastomycosis)†

Not available.

Brucellergen (Brucellosis)†

Not available.

*Candida and Trichophyton Extracts, Combined (Candidiasis)**

- Hollister-Stier, Box 3145, Spokane, WA 99220-3145, telephone (509) 489-5656.
- Berkeley Biologicals, 1831 Second St, Berkeley, CA 94710, telephone (415) 843-6846.
- Iatric Corporation, 2330 South Industrial Park Dr, Tempe, AZ 85282-1893, telephone (602) 966-7248.

*Cat Scratch Fever**

- Unlicensed antigen, available only by special arrangement with D. Paul Robinson, MD, 2121 Park St, Jacksonville, FL 32204, telephone (904) 387-6200.
- Unlicensed antigen, available only by special arrangement with Andrew M. Margileth, MD, Department of Pediatrics, 4301 Jones Bridge Rd, Uniformed Services University of the Health Sciences, Bethesda, MD 20814, telephone (301) 295-3136.

*Coccidioidin**

- Berkeley Biologicals, 1831 Second St, Berkeley, CA 94710, telephone (415) 843-6846.
- Iatric Corporation, 2330 South Industrial Park Dr, Tempe, AZ 85282-1893, telephone (602) 966-7248.

*Cysticercosis**

Not available.

Diphtheria Toxin (for Schick Test)

International Laboratory for Biological Standards, Statens Seruminstitut, Artillerivej 5, DK-2300, Copenhagen S, Denmark, telephone 45-31-952817, Telex 31316 Serum DK, FAX 45-31-955822.

Echinococcin (Casoni)*

Not available.

Filariasis

Not available.

*Histoplasmin**

- Parke-Davis, Division of Warner-Lambert Co, 201 Tabor Road, Morris Plains, NJ 07950, telephone (201) 540-2117 or (800) 223-0432.
- Berkeley Biologicals, 1831 Second St, Berkeley, CA 94710, telephone (415) 843-6846.

Kveim (Sarcoid)

No longer available.

*Leishmaniasis**

Not available.

*S. Benson Werner, "Sources of Supply of Selected Immunobiologics: 1982," *West J Med* 1982; 137:468-470.

†Serologic tests are also available (through local or state health department laboratories).

*Serologic tests are also available (through local or state health department laboratories).

(Werner SB: Sources of supply of selected immunobiologics, 1990. West J Med Nov; 153:503-507)

From the General Infectious Disease Unit, Disease Control Section, California Department of Health Services, Berkeley.

Reprint requests to S. Benson Werner, MD, MPH, Chief, General Infectious Disease Unit, Disease Control Section, California Department of Health Services, 2151 Berkeley Way, Room 708, Berkeley, CA 94704.

Lepromin (Leprosy)

Unlicensed antigen, to be used only for disease classification. Available for use under investigational new drug protocol from Gillis W. Long, Hansen's Disease Center (US Public Health Service), Carville, LA 70721-9607, telephone (504) 642-4704 or (504) 642-4714.

*Lymphogranuloma Venereum (Frei Test)**

Not available.

*Mumps**

Connaught Laboratories, Inc, Route 611, PO Box 187, Swiftwater, PA 18370, telephone (800) VACCINE.

Nocardiosis

Unlicensed skin test preparations (sensitins), prepared from *Nocardia asteroides, Nocardia brasiliensis, Nocardia farcinica,* and *Nocardia otitidis-caviarum,* are available by special arrangement with M. Magnusson, Tuberculin Department, Statens Seruminstitut, Artillerivej 5, DK-2300, Copenhagen S, Denmark, telephone 45-31-952817, Telex 31316 Serum DK, FAX 45-31-955822.

*Q Fever**

Unlicensed antigen, available only by special arrangement, for use in occupational settings (sheep research, slaughterhouse) from Commander, US Army Medical Materiel Development Activity, Attention: Biological Systems, Fort Detrick, Frederick, MD 21701-5011, telephone (301) 663-7661.

Scarlet Fever Toxin (Dick Test)

Not available.

*Schistosomiasis**

Not available.

Skin Test Antigens, Multiple, Combined, for Cellular Hypersensitivity

Included in this category are tetanus toxoid, diphtheria toxoid, *Streptococcus,* old tuberculin, *Candida, Trichophyton,* and *Proteus.*

• Connaught Laboratories, Inc, A Pasteur-Merieux Company, Route 611, PO Box 187, Swiftwater, PA 18370-0187, telephone (800) VACCINE.

*Sporotrichosis**

Not available.

*Toxocara Antigen**

Not available.

*Toxoplasmosis**

Not available.

*Trichinella**

Not available.

*Tularemia**

Not available.

Vaccines

Anthrax

Prepared by and available from Michigan Department of Public Health Laboratories, 3500 North Logan St, Lansing, MI 48914, telephone (517) 373-1290.

*Serologic tests are also available (through local or state health department laboratories).

Bacillus Calmette-Guérin (BCG)

Prepared by Evans Medical Limited, West Sussex, England, and distributed by Quad Pharmaceuticals, Inc, 6340 La Pas Trail, Indianapolis, IN 46288, telephone (800) 222-6925.

Botulinal Toxoid, Pentavalent (A, B, C, D, E)

Unlicensed toxoid produced by the Michigan Department of Public Health Laboratories. Available from the Centers for Disease Control by calling (404) 639-3356 daytime and (404) 639-2888 nights and holidays.

Chikungunya Virus Vaccine, Live, Attenuated

Unlicensed vaccine, available under investigational new drug protocol from the Commander, US Army Medical Research Institute of Infectious Diseases, Fort Detrick, Frederick, MD 21701-5011, telephone (301) 663-2833, FAX (301) 663-2893.

Cytomegalovirus Vaccine

Not commercially available. An unlicensed vaccine is available under investigational new drug protocol from Stanley A. Plotkin, MD, Children's Hospital of Pennsylvania, 34th St and Civic Center Blvd, Philadelphia, PA 19104, telephone (215) 590-2017.

Eastern Equine Encephalitis (EEE) Vaccine, Inactivated

Unlicensed vaccine, available from the Centers for Disease Control by calling (404) 639-3356 daytime and (404) 639-2888 nights and holidays.

Japanese Encephalitis Vaccine

Unlicensed vaccine produced in Japan, China, and Korea. Formerly available from the Centers for Disease Control by calling (404) 639-3356 daytime and (404) 639-2888 nights and holidays, but its use for travel was suspended in the US because of inadequate liability protection for the manufacturer. Travelers may inquire about the availability of the vaccine at American embassies in countries where this mosquito-borne viral encephalitis is endemic. It is likely that the Japanese product (Biken) will be licensed by the US Food and Drug Administration sometime in 1990 and distributed by Connaught Laboratories, Inc, Route 611, PO Box 187, Swiftwater, PA 18370, telephone (800) VACCINE.

Junin Virus Vaccine, Live, Attenuated

Unlicensed vaccine, available under investigational new drug protocol from the Commander, US Army Medical Research Institute of Infectious Diseases, Fort Detrick, Frederick, MD 21701-5011, telephone (301) 663-2833, FAX (301) 663-2893.

Meningococcal Polysaccharide Vaccine, Bivalent (A and C combined) and Tetravalent (A, C, Y, W135 combined)

When meningococcal vaccine is to be used for epidemic control, its release requires approval from the Bureau of Biologics, Food and Drug Administration.

• Prepared by Connaught Laboratories, Inc, Route 611, PO Box 187, Swiftwater, PA 18370, telephone (800) VACCINE.

Mixed Respiratory Vaccine

The mixed respiratory vaccine includes *Staphylococcus aureus, Streptococcus* (viridans and nonhemolytic), *Strep-*

tococcus (Diplococcus) pneumoniae, Branhamella (Neisseria) catarrhalis, Klebsiella pneumoniae, and *Haemophilus influenzae.*

The FDA has directed that further investigation be conducted before this product is determined to be fully effective for the labelled indications.

• Hollister-Stier, Box 3145, Spokane, WA 99220-3145, telephone (509) 489-5656.

Pertussis Vaccine

The Michigan Department of Public Health Laboratories, 3500 N Logan St, Lansing, MI 48909, telephone (517) 373-1290.

Plague

Cutter Biological, Miles Inc, 400 Morgan Lane, West Haven, CT 06516, telephone (203) 937-2000.

Polio, Inactivated (Salk), Enhanced Potency

Connaught Laboratories, Inc, Route 611, PO Box 187, Swiftwater, PA 18370, telephone (800) VACCINE.

Q Fever Vaccine

Unlicensed vaccine, made by the US Army, available under investigational new drug protocol as an investigational product for use in occupational settings (sheep research, slaughterhouse) from Commander, US Army Medical Materiel Development Activity, Attention: Biological Systems, Fort Detrick, Frederick, MD 21701-5011, telephone (301) 663-7661.

Rabies, Purified Chick Embryo Vaccine

Not yet licensed in the US. Available under investigational new drug protocol from Hoechst-Roussel Pharmaceuticals, PO Box 2500, Route 202-206, Somerville, NJ 08876-1258. Contact: Joe Baughman, telephone (201) 231-3947.

Rabies, Duck Embryo Vaccine (DEV) Origin

No longer available.

Rabies, Human Diploid Cell Strain (HDCS) Origin

Connaught Laboratories, Inc, A Pasteur-Merieux Company, Route 611, PO Box 187, Swiftwater, PA 18370-0187, telephone (800) VACCINE.

Rabies, Rhesus Diploid Cell Vaccine

Michigan Department of Public Health Laboratories, 3500 N Logan St, Lansing, MI 48909. Contact: Byron Berlin, telephone (517) 335-8173 or 335-8050.

Rift Valley Fever Vaccine, Inactivated

Unlicensed vaccine, available under investigational new drug protocol from the Commander, US Army Medical Research Institute of Infectious Diseases, Fort Detrick, Frederick, MD 21701-5011, telephone (301) 663-2833, FAX (301) 663-2893.

Rocky Mountain Spotted Fever

Not available.

Smallpox Vaccine

Distribution to civilians was discontinued in May 1983 by the only active US licensed manufacturer (Wyeth Laboratories) of the vaccine. At present, smallpox vaccination is recommended only for the protection of laboratory personnel exposed to smallpox or closely related orthopox viruses (such as monkeypox and vaccinia). Available for administration to eligible employees under the supervision of a physician by calling the Centers for Disease Control at (404) 639-3356 daytime and (404) 639-2888 nights and holidays.

Staphylococcal Vaccine

The FDA has directed that further investigation be conducted before this product is determined to be fully effective for the labelled indication(s).

• Delmont Laboratories, Inc, 715 Harvard Ave, PO Box AA, Swarthmore, PA 19081, telephone (215) 543-3365 or (800) 562-5541.

Tickborne Encephalitis Virus Vaccine

Unlicensed vaccine, available under investigational new drug protocol from the Commander, US Army Medical Research Institute of Infectious Diseases, Fort Detrick, Frederick, MD 21701-5011, telephone (301) 663-2833, FAX (301) 663-2893.

Tularemia Vaccine, Live, Attenuated

Unlicensed vaccine available from the Centers for Disease Control by calling (404) 639-3356 daytime and (404) 639-2888 nights and holidays. An unlicensed live-attenuated vaccine for laboratory personnel working with *Francisella tularensis* is available from the US Army Medical Materiel Development Activity, Attention: SGRD-UMB, Fort Detrick, Frederick, MD 21701-5009, telephone (301) 663-7661.

Typhoid Vaccine, Live, Oral, Strain Ty 21a ("Vivotif Berna" [R] Vaccine)

Produced by Swiss Serum and Vaccine Institute, Rehagstrasse 79, PO Box 2707, 3001 Berne, Switzerland, telephone (011) 41-31-34-4111. Available in the US from Berna Products Corporation, Coral Gables, FL 33134, telephone (305) 443-2900.

Typhus

Not available.

Vaccinia Vaccine

See smallpox vaccine above.

Varicella Zoster Vaccine

Not commercially available in the US but available for clinical trials from C. Jo White, MD (clinical monitor), Merck, Sharp & Dohme Research Laboratories, Sumneytown Pike, West Point, PA 19486, telephone (215) 834-2554.

Venezuelan Equine Encephalitis Vaccine, Live, Attenuated

Unlicensed vaccine available from the Centers for Disease Control by calling (404) 639-3356 daytime and (404) 639-2888 nights and holidays.

Western Equine Encephalitis Virus Vaccine, Inactivated

Unlicensed vaccine, available under investigational new drug protocol from the Commander, US Army Medical Research Institute of Infectious Diseases, Fort Detrick, Frederick, MD 21701-5011, telephone (301) 663-2833, FAX (301) 663-2893.

Yellow Fever

Connaught Laboratories, Inc, Route 611, PO Box 187, Swiftwater, PA 18370, telephone (800) VACCINE, to state-

registered Yellow Fever Vaccination Centers authorized to purchase vaccine.

Antitoxins and Immunoglobulins

Bolivian Hemorrhagic Fever Immune Globulin

Unlicensed immune globulin, available under investigational new drug protocol from the Commander, US Army Medical Research Institute of Infectious Diseases, Fort Detrick, Frederick, MD 21701-5011, telephone (301) 663-2833, FAX (301) 663-2893.

Botulism Antitoxin (Equine) (Trivalent A, B, E)

Connaught Laboratories Limited, 1155 Steeles Ave W, Willowdale, Ontario, Canada. Available from California Department of Health Services, Disease Control Section, by supply from Division of Host Factors, Center for Infectious Disease, Centers for Disease Control (CDC). There are also emergency stockpiles stored at Public Health Service Quarantine Stations in the US that may be released by request of the Division of Bacterial Diseases, Center for Infectious Disease, CDC. The daytime number is (404) 639-3753, and the night and holiday number is (404) 639-2888.

Cytomegalovirus Immune Globulin, Intravenous (Human)

Massachusetts Public Health Biologic Laboratories, 305 South St, Boston, MA 02130, telephone (617) 522-3700, extension 264. Licensed by the Food and Drug Administration for prevention of serious cytomegalovirus disease in recipients of kidney transplants.

Diphtheria Antitoxin (Equine)

- Connaught Laboratories, Inc, Route 611, PO Box 187, Swiftwater, PA 18370, telephone (800) VACCINE.
- Sclavo, Inc, 5 Mansard Court, Wayne, NJ 07470, telephone (201) 696-8300 or (800) 526-5260. (Production has been discontinued; quantity is limited to warehouse supplies.)

There are emergency stockpiles stored at Public Health Service Quarantine Stations in the US that can be released by calling the Centers for Disease Control at (404) 639-3091 daytime and (404) 639-3356 nights and holidays.

Eastern Equine Encephalitis (EEE), Immune Plasma, Human

Unlicensed immune plasma available from the Centers for Disease Control by calling (404) 639-3356 daytime and (404) 639-2888 nights and holidays.

Gas Gangrene, Polyvalent

Not available in the US (Servier Laboratories, Ltd, England).

Immune Globulin, Intravenous, Human

- Baxter Healthcare Corporation, Hyland Division, 550 North Brand Blvd, Glendale, CA 91203, telephone (818) 956-3200 or (800) 423-2090.
- Cutter Biological, Miles Inc, 400 Morgan Lane, West Haven, CT 06516, telephone (203) 937-2000.
- Armour Pharmaceutical Company, 920 A Harvest Dr, Blue Bell, PA 19422, telephone (215) 540-8106.
- Alpha Therapeutic Corporation, 5555 Valley Blvd, Los Angeles, CA 90032, telephone (800) 421-0008, (800) 851-8891, or (213) 225-2221.

Mumps Immune Globulin

No longer available.

Pertussis Immune Globulin (Human)

No longer available.

Rabies Antiserum (Equine Origin)

Because of a significantly lower incidence of adverse reactions, human rabies immune globulin (RIG, below) is preferred over antirabies serum of equine origin.

- Sclavo, Inc, 5 Mansard Court, Wayne, NJ 07470, telephone (201) 696-8300 or (800) 526-5260. (Production has been discontinued; quantity is limited to warehouse supplies.)

Rabies Immune Globulin (RIG) (Human Origin)

- Cutter Biological, Miles Inc, 400 Morgan Lane, West Haven, CT 06516, telephone (203) 937-2000.
- Connaught Laboratories, Inc, A Pasteur-Merieux Company, Route 611, PO Box 187, Swiftwater, PA 18370-0187, telephone (800) VACCINE.

St Louis Encephalitis (SLE), Immune Plasma, Human

Unlicensed immune plasma, available from the Centers for Disease Control by calling (404) 639-3356 daytime and (404) 639-2888 nights and holidays.

Snake Antivenin (Equine), Crotalidae, Polyvalent

Wyeth Laboratories, Wasp and Biddle Sts, Marietta, PA 17547, telephone (717) 426-1941.

Snake Antivenin (Equine), North American Coral Snake (Micrurus fulvius)

Wyeth Laboratories, Wasp and Biddle Sts, Marietta, PA 17547, telephone (717) 426-1941.

Spider Antivenin (Equine), Black Widow Spider

Merck, Sharp & Dohme, Sumneytown Pike, West Point, PA 19486, telephone (215) 661-5000.

Staphylococcal Antitoxin

Not available.

Tetanus Antitoxin, (Equine Origin)

Tetanus immune globulin, of human origin, is preferred for the prevention and treatment of tetanus; tetanus antitoxin should be used only when tetanus immune globulin is not available.

- Sclavo, Inc, 5 Mansard Court, Wayne, NJ 07470, telephone (201) 696-8300 or (800) 526-5260. (Production has been discontinued; quantity is limited to warehouse supplies.)

Tetanus Immune Globulin

Cutter Biological, Miles Inc, 400 Morgan Lane, West Haven, CT 06516, telephone (203) 937-2000.

Vaccinia Immune Globulin (VIG)

This is a licensed product (Hyland Laboratories) dispensed only for the treatment of eczema vaccinatum, vaccinia necrosum, or ocular or generalized vaccinia in the few people who receive smallpox vaccine. Available from the Centers for Disease Control by calling (404) 639-3356 daytime and (404) 639-2888 nights and holidays.

Varicella-Zoster Immune Globulin (VZIG)

Massachusetts Public Health Biologic Laboratories, 305 South St, Boston, MA 02130, telephone (617) 522-3700 and distributed in Massachusetts by the producer and elsewhere in the US and Canada by the American Red Cross Blood Services—Northeast Region, through 18 regional blood centers. For further information on the center serving your area, call (617) 731-2130 or (617) 734-4430, 24 hours a day; in California: San Jose (408) 292-6242 and Los Angeles (213) 384-5261.

Venezuelan Equine Encephalitis (VEE), Immune Plasma, Human

Unlicensed immune plasma, available from the Centers for Disease Control by calling (404) 639-3356 daytime and (404) 639-2888 nights and holidays.

Western Equine Encephalitis (WEE), Immune Globulin, Human

Unlicensed immune globulin, available from the Centers for Disease Control by calling (404) 639-3356 daytime and (404) 639-2888 nights and holidays.

Adult Respiratory Distress Syndrome During Pregnancy and Immediately Postpartum

JOSEPH L. SMITH, MD, *Danville, Pennsylvania;* FRANK THOMAS, MD; JAMES F. ORME, Jr, MD; *and* TERRY P. CLEMMER, MD, *Salt Lake City, Utah*

From 1976 to 1983, the adult respiratory distress syndrome occurred in 14 patients during pregnancy or within a month postpartum. There were 8 survivors, giving a 43% mortality. All but 2 patients had obstetric-related precipitating events—labor problems, infections, eclampsia-toxemia, and obstetric hemorrhages. During emergency cesarean sections, 3 patients had respiratory problems that may have caused their respiratory distress syndrome. The average duration of mechanical ventilatory support was 16 days. Six patients had barotrauma with 1 patient sustaining an irreversible anoxic central nervous system injury. Infections were documented in 8 patients, 6 of whom had obstetric foci. There is a lack of information regarding the adult respiratory distress syndrome in this patient group. Though uncommon, it can cause substantial mortality and morbidity.

(Smith JL, Thomas F, Orme JF Jr, Clemmer TP: Adult respiratory distress syndrome during pregnancy and immediately postpartum. West J Med 1990 Nov; 153:508-510)

The adult respiratory distress syndrome (ARDS) remains a serious medical problem.[1] It has substantial effects on young women who are pregnant or immediately postpartum,[2] causing their families to suffer as well. To understand conditions associated with ARDS in this patient group, we reviewed case records of patients we saw over a seven-year period (July 1976 through June 1983).

Patients and Methods

Daily patient admission logbooks from the respiratory and shock or trauma intensive care units of the LDS Hospital, Salt Lake City, Utah, were retrospectively reviewed to identify cases of ARDS occurring in female patients ages 17 to 45. The syndrome was defined by criteria reported by Ashbaugh and co-workers and modified to include pulmonary artery wedge pressures of less than 18 mm of mercury.[3] The medical records of those who satisfied these screening criteria were reviewed to determine whether they were pregnant or if they had been delivered of a baby within a month of admission to our intensive care units (ICUs). Records of patients satisfying these criteria were further analyzed for demographic information, details of their obstetric history, preexisting remote or active medical or surgical conditions, acute obstetric and nonobstetric medical and surgical problems, the duration of mechanical ventilatory support, complications of care including infections, and mortality.

Results

A total of 14 cases of the adult respiratory distress syndrome were identified in this patient group (Table 1). There were eight survivors and six nonsurvivors, representing a 43% mortality rate for these patients. Nine patients were referred to our hospital for care after the onset of ARDS, and the other five received their initial obstetric care at our hospital. During this seven-year study period (1976 to 1983), there were 47,198 pregnancy-related admissions to our hospital.

The overall average age was 26 years, which was similar to the average ages for both survivors and nonsurvivors. Most patients were in their mid-20s, with only two exceeding 30 years of age.

In all but three patients, ARDS developed in the last trimester of pregnancy. The average gestational age was 30 weeks. The survivors' average gestational age was 32 weeks versus 26 weeks for the nonsurviving group. Three (50%) nonsurvivors and two (25%) survivors had problems with previous pregnancies. One nonsurvivor apparently was unaware of her pregnancy. The average ratio of gravidity to parity was 3:1, with only four patients being primigravidas.

One survivor and three nonsurvivors had active medical problems. In two nonsurvivors, these problems—alcoholism and diabetes mellitus with hypertension—may have contributed to their acute obstetric problems.

The presumed causes of the adult respiratory distress syndrome are also listed in Table 1. For 12 patients (86%)—6 survivors and all 6 nonsurvivors—the initial problems were obstetric. These were evenly divided into four broad categories: labor problems, obstetric infections, eclampsia-toxemia, and hemorrhage. The major accompanying problems were respiratory complications—gastric aspiration (2 patients) and respiratory arrest (1; this patient also had abruptio placentae)—all anesthesia associated during emergency cesarean section, amnionitis, possible amniotic fluid emboli, and eclampsia. Only two patients received tocolytic therapy for premature labor. Both experienced one of the mentioned respiratory complications. Two patients (14%) initially had problems that were nonobstetric. One was a motor vehicle accident victim with facial and chest injuries, and the other had acute cholecystitis and pancreatitis that precipitated other problems, including eclampsia.

The duration of mechanical ventilatory support was

ABBREVIATIONS USED IN TEXT

ARDS = adult respiratory distress syndrome
ICU = intensive care unit

From the Division of Critical Care Medicine, LDS Hospital, and Division of Respiratory, Critical Care, and Occupational (Pulmonary) Medicine, University of Utah School of Medicine, Salt Lake City. Dr Smith is currently with the Geisinger Medical Center, Danville, Pennsylvania.

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TABLE 1.—*Adult Respiratory Distress Syndrome (ARDS) in Young Pregnant or Postpartum* Women*

Patient	*Age, yr*	*G:P Ratio†*	*Gestation, wk*	*Preexisting or Previous Medical Conditions*	*Cause of ARDS*	*Ventilator Support, d*	*Infections or Complications (Treatment)*
Survivors							
1	26	15:0 (Habitual abortions)	31	None	Acute cholecystitis-pancreatitis; eclampsia	14	Peritonitis and lesser sac abscess: *Escherichia coli*, *Candida* sp, *Staphylococcus epidermidis* (surgical drainage)
2‡	26	1:1	30	History of hookworm infestation, with dyspnea and hemoptysis	Toxemia, cesarean section; gastric aspiration during cesarean section	48	*Pseudomonas aeruginosa* bacteremial sepsis × 2, necrotic uterus and pelvic abscess (hysterectomy and drainage of abscess); maxillary sinusitis, acute cholecystitis (sinus drainage and cholecystectomy); pneumothoraces × 10
3‡	31	3:2	17	None	Abruptio placentae, shock; amnionitis	7	Non-group A/B β-streptococcal endometritis and myometritis (hysterectomy, bilateral salpingo-oophorectomy); intracerebral hemorrhages × 2; acute renal failure
4‡	27	3:0 (Spontaneous abortion × 3)	35	History of heart murmur	Amnionitis	26	Non-group A/B β-streptococcal amnionitis, endometritis, and myometritis with uterine abscess and pelvic abscess (hysterectomy and right salpingo-oophorectomy); tension pneumothoraces
5	30	3:2	32	Hyperthyroidism; history of ovarian cysts	Premature labor, tocolytic therapy; abruptio placentae with uterine hemorrhage; shock and respiratory arrest during cesarean section	9	Endometritis, pelvic thrombophlebitis (exploratory laparotomy with hysterectomy and bilateral salpingo-oophorectomy); wound dehiscence
6‡	23	1:0	Term	None	Arrest of labor; cesarean section	22 (ECMO × 72 h)	Empyema (drained)
7‡	29	2:2	Term (home delivery)	None	Retained placenta with uterine hemorrhage, shock, and DIC; pneumonia	2	
8	20	1:0	32	None	Trauma (facial, chest contusions)	21	
Average	26.5	≅4:1	32			≅19	
Nonsurvivors							
9‡	25	§	27 (estimated)	History of GI bleeding; alcoholism	*Bacteroides* sp bacteremia and sepsis due to endometritis; dental abscess	1	Endometritis; dental abscess; hepatic necrosis from herpes simplex type II hepatitis (abscessed tooth excised; hysterectomy, bilateral salpingo-oophorectomy); shock syndrome with hepatic failure, acute renal failure, and DIC
10‡	26	5:2‖	Term (postpartum)	Asthma	*E coli* endometritis; ? influenza	9 (ECMO × 8 d)	Endometritis; myocardial infarction; GI bleed; seizures; retroperitoneal hematoma (massive transfusion, 115 units RBCs); renal failure
11	26	2:0¶	24	Insulin-dependent diabetes mellitus; hypertension (being treated); esophageal strictures, previous esophageal rupture	Eclampsia	45	Multiple organ system failure; pulmonary fibrosis; recurrent pneumothoraces
12	28	3:2‖	30	None	Premature labor, tocolytic therapy; gastric aspiration during intubation for cesarean section	19	Anoxic brain injury due to shock caused by bilateral tension pneumothorax
13‡	21	1:0	29	None	Eclampsia	45	Multiple organ system failure; bilateral tension pneumothoraces
14‡	24	2:1	6	None	Spontaneous abortion; shock, ? amniotic fluid emboli	2	Shock; tension pneumothorax; DIC; renal and hepatic failure
Average	25	3:1	26			≅20	
Group averages							
	≅26	3:<1	29.5			19	

DIC = disseminated intravascular coagulation, ECMO = extracorporeal membrane oxygenation, GI = gastrointestinal, RBCs = erythrocytes [red blood cells]

*Within a month of delivery.
†Gravidity to parity ratio.
‡Transported to LDS Hospital for care.
§Patient was unaware of pregnancy; delivered of a 900-gram fetus a week before admission.
‖Patient had 1 or more previous cesarean sections for a transverse lie.
¶Conceptus from previous pregnancy lost at 7 months.

similar for both groups, averaging 19 to 20 days. For the four nonsurvivors who did not die within one to two days, however, the mean duration of mechanical ventilatory support was 30 days—11 days longer than for the survivors. Of note, two patients were participants in an earlier national Extracorporeal Membrane Oxygenation Study.[4] Six patients had barotrauma manifesting as tension pneumothoraces. The shock associated with this complication caused substantial irreversible anoxic brain injury in one patient. Several patients had more than one pneumothorax, necessitating the simultaneous use of multiple chest tubes.

Eight patients—six (75%) survivors and two (33%) nonsurvivors—had definable and treatable foci of infections either as an inciting event or as a complication of care. In the survivor group, four patients had obstetric foci of infection: three cases of amnionitis or endometritis and one of pelvic abscess. In the patient with a pelvic abscess, other distant foci of infection developed as well. Other infections in the survivor group included empyema and lesser sac abscess. Only two nonsurvivors had definable infections: both had endometritis from which one died acutely of septic shock. In two other nonsurvivors multiple organ system failure developed, but no septic foci were found.

The nonsurvivors were grouped into early and late (after two days of ICU care) deaths. The two patients in the early-death group died of fulminant shock syndromes, which included disseminated intravascular coagulation and hepatic and renal failure. Four patients were in the late-death group. One patient died on her ninth day in the ICU of sepsis, cardiac failure, and renal failure. While receiving extracorporeal membrane oxygenation, she was given a massive number of transfusions—115 units of packed erythrocytes—which may have contributed to her organ failures and death. On the 19th day in the ICU, life support was withdrawn from one patient who had sustained anoxic central nervous system injury from shock and hypoxemia associated with simultaneously occurring bilateral tension pneumothoraces. Two patients died on their 45th day in the ICU of irreversible respiratory failure associated with progressive multiple organ system failure. Only one autopsy was carried out in these six patients. The additional finding of hepatic necrosis from herpes simplex type 2 hepatitis was discovered in the first nonsurvivor (patient 9, Table 1).

Discussion

Although the respiratory distress syndrome in pregnant and immediately postpartum patients is uncommon, when it occurs, it is from clinical conditions associated with catastrophic events. These events are complex, with manifestations of multiple organ system involvement, but seem to stem primarily from obstetric problems and occur mainly in the last trimester of pregnancy.

Whether as an initial event or a complication of this event or care, infections contribute to the development of ARDS.[5,6] Our results substantiate these findings and extend them to include obstetric patients. When infections are defined and treated, patients' survivability seems enhanced. This underscores the need to search intensively for sources of infection. As our experience shows, the initial search must include the pelvic structures for they were the source of 75% of the infections.

The causes of ARDS during pregnancy listed in this report are similar to those reported by others.[7,8] Our report groups many of the various causes and notes their relative significance. Most problems (86%) were obstetric in origin and surprisingly evenly distributed over four categoric groupings. For several patients, however, the accompanying problem may have been the main cause of ARDS, particularly where it was a respiratory complication. All of the accompanying respiratory problems occurred during anesthesia for emergency cesarean sections and accounted for 50% of all major accompanying events. Gastric aspiration was the most frequent respiratory complication. Because the morbidity and mortality from this disorder has remained unchanged over the past several decades, the risk factors for and the prevention and management of this problem need to be completely understood by physicians caring for these patients.[9] Also, gastric aspiration is the most likely explanation for the two patients who received tocolytic therapy for premature labor. Recent evidence suggests that the pulmonary edema associated with tocolytic therapy is hydrostatic-pressure induced.[10]

Complications of prolonged mechanical ventilatory support were evident in our patients. Barotrauma was a recurrent problem that contributed to the death of at least one patient. This problem is currently neither predictable nor preventable. Physicians caring for patients receiving mechanical ventilatory support must be vigilant in anticipating this problem and possess the necessary skills to manage it.

The causes of our patients' deaths are categorically similar to those reported by Montgomery and associates.[11] Those patients who died within 72 hours of admission died of their presenting shock syndromes. The patients who died after 72 hours died of complications of their care or with various combinations of the sepsis syndrome; cardiac, renal, central nervous system, and hepatic dysfunction; or unremittent respiratory failure. Likewise, our patients' mortality rate (43%) is similar to that of other recently reported ARDS series.[11,12] Unfortunately for this patient group, where the tragedy of losing a young mother may have far-reaching socioeconomic and developmental effects on a family, this rate is unacceptably high. As new therapeutic modalities and insights regarding the pathogenesis of ARDS are introduced into clinical medicine, mortality should be reduced. Our report suggests that some benefit might be realized by better control of the sepsis syndrome.

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Recent Trends in Cesarean Section Use in California

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This paper was chosen as the runner-up in THE WESTERN JOURNAL OF MEDICINE's 1990 Medical Student Writing Competition. The contest was open to all students attending medical schools in the West and will be repeated annually.

LINDA HAWES CLEVER, MD
Editor

Cesarean section use in the United States has increased to 24.7% of deliveries in 1988 and is the most common hospital surgical procedure. California cesarean section rates were examined to measure recent trends in obstetric practices and to project future patterns of cesarean section use. Using discharge abstracts from 1983 to 1987 California hospital deliveries, total cesarean section rates were found to increase from nearly 22% in 1983 to 25% in 1987, an increase of 15%. Using a series of least-squares regression models, time trends in the distribution of indications associated with cesarean section among all deliveries and indication-specific cesarean section rates were evaluated. Increases in the number of women with previous cesarean section and fetal distress contributed to rising cesarean section rates. In addition, indication-specific cesarean section rates increased for breech presentation and dystocia. These trends were counterbalanced, in part, by declining rates of repeat cesarean sections. Trends noted for July 1985 through 1987 did not differ substantially from those observed for January 1983 to June 1985, suggesting that recent policy attempts to alter cesarean section use have not had a measurable effect on existing trends. Projections suggest that California cesarean section rates will rise to a level of 34% by the year 2000.

(Stafford RS: Recent trends in cesarean section use in California. West J Med 1990 Nov; 153:511-514)

In the past 20 years cesarean section use has increased dramatically to become the most common surgical procedure in United States hospitals.[1] While in 1970 only 5.5% of US deliveries were by cesarean section, the 1988 cesarean section rate was 24.7%.[2] The National Center for Health Statistics has projected a cesarean section rate of 40% by the year 2000.[3] Increases in cesarean section use have been accompanied by concerns regarding maternal and perinatal outcome and health care costs.[4] Doubts regarding the appropriateness of current trends have led to persistent attempts to modify practice patterns.[4,5] While the presumed failure of these strategies has been asserted,[6,7] between 1986 and 1988 US cesarean section rates only increased from 24.1% to 24.7%[2] A more detailed examination of this slowing rate of increase, however, suggests the potential for renewed increases in the future.

To fill the need for a current assessment of trends in cesarean section use, California cesarean section rates are examined using 1983 to 1987 hospital discharge abstract data. Past research indicates that cesarean sections are carried out for a heterogeneous set of clinical indications, including a previous cesarean section, breech presentation, dystocia, fetal distress, and other indications. In this report I analyze each of these indications through a series of regression models that measure time trends in the relative frequency of obstetric indications and indication-specific cesarean section rates. This process allows an evaluation of whether cesarean section rates are now rising more slowly and enables the projection of future patterns of obstetric practice.

Methods

Hospital Discharge Data

The Office of Statewide Health Planning and Development collects information on every nonmilitary hospital discharge in California.[9] These data were available for 1983 through 1987 and include between 401,901 and 483,535 annual deliveries. The mode of delivery was determined by diagnosis-related group codes 370 through 371 (cesarean sections) and 372 through 375 (vaginal deliveries). Cesarean section rates were calculated as the number of cesarean sections per 100 deliveries. Diagnostic information was available as codes of the *International Classification of Diseases,* ninth revision (ICD-9-CM).[10] To account for deliveries with more than one diagnosis, a widely employed hierarchy of mutually exclusive primary indications was adopted for this analysis.[11,12] From highest to lowest priority, these were as follows: previous cesarean section (ICD-9-CM code 654.2), breech presentation (652.2 and 669.6), dystocia (653 and 660 to 662, except 661.3), fetal distress (656.3), all other indications (other codes in 642 to 663, and 669, except 669.1 to 669.5), and no reported indications. When more than one indication was present for a delivery, the highest priority diagnosis was assigned regardless of its order on the discharge abstract. For example, those deliveries defined as a breech presentation exclude cases of breech presentation occurring in women with previous cesarean sections. The small number of cesarean sections without a reported indication (461 deliveries in 1987) are included in the actual and projected total cesarean section rates but are not displayed separately.

This research was supported by grant No. HS-06116 from the National Agency for Health Care Policy and Research.

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Statistical Methods

Time trends in yearly and monthly cesarean section rates were determined according to the date of admission. Patterns of cesarean section use were dissected into two components: the relative frequency of indications often associated with cesarean section (how frequently a condition occurs among all deliveries), and indication-specific cesarean section rates (the rate of cesarean section given the occurrence of a condition).[12] For greater precision in analyzing time trends, separate statistical analyses were done for these two components. This allowed the analysis to account for the distinct trends in cesarean section use present for different clinical indications.

To measure the statistical significance of trends in cesarean section use, a series of regression models was developed on an indication-specific basis. The month was used as the independent variable to predict the relative frequency of indications associated with cesarean section and indication-specific cesarean section rates. Because both relative frequency and cesarean rates must take values between 0% and 100%, it was necessary to algebraically transform these figures so that future projections would fall within this range. Rates and frequencies were transformed into logits for the regression, so that, for example:

$$\log_e \{[P(CS)]/[1-P(CS)]\} = b_0 + b_1 \cdot \text{month},$$

where $P(CS)$ is the indication-specific probability of cesarean section. A positive coefficient indicates an increasing cesarean rate (or relative frequency), and a negative coefficient indicates a decreasing cesarean rate (or relative frequency). A weighted least-squares method was used to estimate the regression equations.[13]

Three sets of regression equations were estimated: 30 months of data from January 1983 to June 1985, 30 months of data from July 1985 to December 1987, and 60 months of data from 1983 through 1987. The estimated annual percentage change in the cesarean section rate (or relative frequency) was calculated from each regression equation at the midpoint of the time period covered by the equation. These figures were compared to assess whether the more recent 1985 to 1987 trends differed from those for the earlier 1983 to 1985 period. Because the obstetric indications were defined in a mutually exclusive and hierarchic manner, regression models for the relative frequency of indications used denominators that excluded deliveries in higher priority categories. For example, in the regression models the relative frequency of breech presentation was calculated for deliveries other than those with a previous cesarean section.

Future patterns of cesarean section use through 2000 were estimated by extrapolating from the indication-specific regression equations based on the entire 1983 to 1987 data (60 months). Although there is a great deal of statistical uncertainty associated with these projections, they provide a useful estimate of where current practice patterns may be leading. The total cesarean section rate for 2000 was projected by aggregating by individual indications associated with cesarean section.

Results

The total cesarean section rate in California increased from 21.7% in 1983 to 25.0% in 1987, an increase of 15.2%. Monthly rates ranged from 20.9% in January1983 to 25.4% in June 1987. Consistent with national estimates,[2] the increase in total cesarean section rates from 24.5% in 1986 to 25.0% in 1987 was smaller than in preceding years. Time trends in the proportion of deliveries with a particular indication and indication-specific cesarean section rates varied by indication. Although cesarean section rates increased for most indications, declining indication-specific rates were noted for women with previous cesarean sections. Trends noted for 1985 to 1987 did not differ greatly from those observed for 1983 to 1985. Projections by the specific indications associated with cesarean section suggest that by 2000 the cesarean section rate in California will rise to 33.7%.

Previous Cesarean Section

The occurrence of deliveries to women with previous cesarean sections increased from 8.6% of all deliveries in 1983 to 10.2% in 1987 (Table 1). Monthly increases in the relative frequency of previous cesarean sections were similar for 1985 to 1987 compared with 1983 to 1985. Cesarean section rates in women with previous cesarean sections, however, decreased between 1983 and 1987 (Table 2). In 1983, 93.0% of women with previous cesarean sections were delivered by another cesarean section, but by 1987, the repeat cesarean section rate was 87.4%. Monthly time trends in repeat cesarean section rates were statistically

TABLE 1.—*Relative Frequency of Obstetric Indications Among All Hospital Deliveries, California, 1983 to 1987*

		Deliveries With a Specific Indication/100 Total Deliveries						
Year	Number of Deliveries	Previous Cesarean Section	Breech Presentation	Dystocia	Fetal Distress	Other Indications	No Indications	Total
1983	401,901	8.6	3.1	11.1	5.7	21.2	50.3	100.0
1984	405,927	9.1	3.1	11.4	6.9	22.4	47.1	100.0
1985	444,908	9.2	3.1	11.7	8.0	23.3	44.7	100.0
1986	461,569	9.9	3.0	12.2	8.5	24.0	42.4	100.0
1987	483,535	10.2	3.1	12.5	8.2	24.8	41.3	100.0
Projected 2000*		18	3	17	22	26	14	100
Regression 1983 to 1985†								
Annual percentage change, %		5.1	0.0	3.3	21.0	8.6		
(95% confidence limits)		(3.4, 6.9)	(−1.3, 1.4)	(2.3, 4.3)	(19, 23)	(7.5, 9.6)		
Regression 1985 to 1987‡								
Annual percentage change, %		5.3	2.1	3.8	0.4	4.3		
(95% confidence limits)		(4.0, 6.7)	(0.8, 3.4)	(2.7, 4.9)	(−2.4, 3.2)	(3.5, 5.1)		

*Projected proportions of each indication as a proportion of all deliveries are derived from regression equations based on 1983 to 1987 data.
†Based on regression equations in the form of $\log_e$ [proportion/(1−proportion)] = $b_0 + b_1 \cdot$ month, for 30 months from January 1983 to June 1985.
‡Based on regression equations in the form of $\log_e$ [proportion/(1−proportion)] = $b_0 + b_1 \cdot$ month, for 30 months from July 1985 to December 1987.

TABLE 2.—*Cesarean Section Rates by Indication, Hospital Deliveries, California, 1983 to 1987*

Year	Cesarean Sections/100 Deliveries With a Specific Indication					
	Previous Cesarean Section	Breech Presentation	Dystocia	Fetal Distress	Other Indications	Total
1983	93.0	81.9	62.2	30.2	11.8	21.7
1984	91.4	82.6	62.3	28.9	11.3	22.6
1985	89.9	85.6	62.8	27.8	11.6	23.2
1986	89.2	86.9	64.4	28.5	11.5	24.5
1987	87.4	87.0	63.8	30.6	11.5	25.0
Projected 2000*	50	96	70	32	11	34
Regression 1983 to 1985						
Annual percentage change, %†	−1.6	1.9	0.1	−4.6	−1.9	
(95% confidence limits)	(−2.0, −1.2)	(1.0, 2.7)	(−0.7, 0.7)	(−6.7, −2.4)	(−3.7, −0.2)	
Regression 1985 to 1987						
Annual percentage change, %‡	−1.4	0.7	0.1	6.9	−1.1	
(95% confidence limits)	(−1.9, −0.9)	(0.1, 1.3)	(−0.6, 0.8)	(4.0, 10.0)	(−2.6, 0.3)	

*Projected indication-specific cesarean section rates are derived from regression equations based on 1983 to 1987 data.
†Based on regression equations in the form of $\log_e$ [rate/(1−rate)] = $b_0 + b_1 \cdot$ month, for 30 months from January 1983 to June 1985.
‡Based on regression equations in the form of $\log_e$ [rate/(1−rate)] = $b_0 + b_1 \cdot$ month, for 30 months from July 1985 to December 1987.

significant and similar for 1983 to 1985 compared with the more rapid declines for 1983 to 1985.

Breech Presentation

Between 1983 and 1987, the occurrence of breech presentation remained close to 3.1% of deliveries (Table 1). The rates of cesarean section for breech presentation increased from 81.9% in 1983 to 87.0% in 1987 (Table 2). A regression analysis of monthly trends indicated that increases in cesarean section rates for breech presentation between 1985 and 1987 were slower than those from 1983 to 1985.

Dystocia

Because dystocia is a subjective diagnosis, the reported frequency of dystocia is itself an important indicator of practice patterns.[4] Between 1983 and 1987, the occurrence of dystocia increased from 11.1% to 12.5% (Table 1). The most recent trends (1985 to 1987) were not significantly different from the trends for 1983 to 1985.

Statistically significant increases in cesarean section rates for dystocia were observed from 1983 (62.2%) to 1987 (63.8%), although trends within each 30-month period were not statistically significant (Table 2). In addition, no differences in trends for 1985 to 1987 and 1983 to 1985 were noted. The increases in both the occurrence of dystocia and dystocia-specific cesarean section rates show that this indication has made a sizable contribution to increases in the total cesarean section rate between 1983 and 1987.

Fetal Distress

The relative frequency of fetal distress increased from 5.7% of all deliveries in 1983 to 8.2% in 1987, although the regression analysis indicates that there has been a slowing of this increase in 1985 to 1987 compared with 1983 to 1985 (Table 1). Cesarean section rates for fetal distress decreased from 30.2% in 1983 to 27.8% in 1985, then increased to 30.6% by 1987 (Table 2). Like dystocia, fetal distress is a subjective diagnosis.[4] Fluctuating cesarean section rates for fetal distress combined with the more frequent reporting of fetal distress suggest that this indication also has contributed to rising total cesarean section rates.

Other Indications

The occurrence of other indications associated with cesarean section has increased from 21.2% in 1983 to 24.8% in 1987 (Table 1). Based on the regression analysis, the magnitude of this increase was less dramatic for 1985 to 1987 compared with 1983 to 1985. Cesarean section rates in the presence of other indications have remained approximately constant (Table 2).

Projection of Future Cesarean Section Rates

Based on the trends for the entire 1983 to 1987 period, statistical projections suggest that future cesarean section rates will continue to increase, reaching a rate of 34% by the year 2000 (Figure 1, Table 2). This figure represents the aggregation of individual projections of relative frequency of indications and indication-specific cesarean section rates (Tables 1 and 2). The projected rate of increase from 1987 to 2000 is considerably slower than observed during the 1983 to 1987 period, largely because of projected decreases in repeat cesarean section rates.

Discussion

Between 1983 and 1987, cesarean section rates in California increased from 21.7% to 25.0%, representing the continuation of previously noted trends.[2,7,12] These results are of particular interest given the widespread dissemination of research questioning the clinical rationale for increasing cesarean section use.[14] When the data of the 30 months from July 1985 to December 1987 are compared with those of the 30 months from January 1983 to June

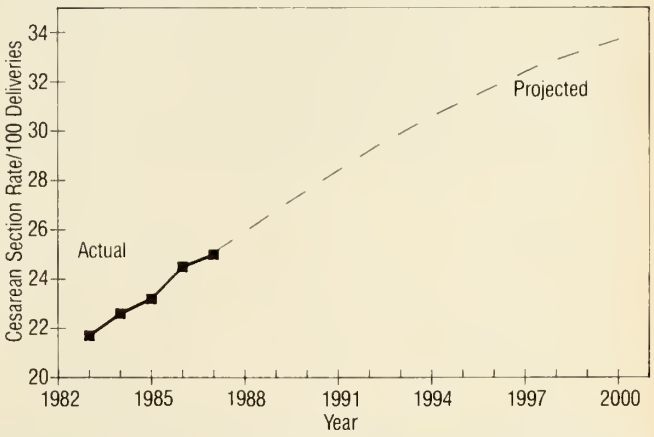

Figure 1.—Actual (1983 to 1987) and projected (1988 to 2000) total cesarean section rates are shown per 100 California hospital deliveries. Projected rates are based on indication-specific regression analysis of 1983 to 1987 data.

1985, there is no convincing evidence that the most recent trends deviate from earlier trends. The increasing prominence of health policy strategies attempting to alter cesarean section use has not had a dramatic effect on these recent trends.

Projecting future practice patterns suggests that total cesarean section rates will increase less rapidly than in the past. This slowing rate of increase is due to decreasing repeat cesarean section rates, which will become increasingly important as the number of women with previous cesarean sections increases. In addition, there are mathematic limits on the extent to which the relative frequency of indications associated with cesarean section can increase. Currently just under 50% of deliveries have an indication associated with cesarean section.

The projected total cesarean section rate of 34% in 2000 is considerably lower than the projection of 40% made by the National Center for Health Statistics.[3] The lower rate projected in this study results from its more detailed analysis of specific indications associated with cesarean section and illustrates the limitations of emphasizing aggregate linear trends. The projections made in this report have taken into account the finding that trends in cesarean section use vary with different clinical indications.

The close parallel between California and national trends[15] makes it likely that these results approximate patterns for the nation as a whole. The large number of deliveries in California (13% of all 1987 deliveries in the US) allows for the reliable estimation of current obstetric practice patterns, but the use of hospital discharge abstracts to monitor and project obstetric practice patterns is not without its limitations. Although the data are relatively recent, the use of data through 1987 does not reflect changes in cesarean section use that may have occurred in the past three years. In addition, the uniformity and reliability of the reporting of indications associated with cesarean section may be less than optimal. The increased reporting of fetal distress and dystocia, for example, is likely to reflect the subjective nature of diagnosing these conditions rather than objective changes in the obstetric population.[4] Although the projections are based on only five years of data, the trends during 1983 to 1987 are consistent with earlier patterns of increasing cesarean rates.[15]

The methods used to project future patterns of cesarean section use assume that the 1983 to 1987 trends will continue unchanged into the future. Therefore, this study's projections do not account for recent or future policy strategies aimed at reducing cesarean section use.[5] Given the likelihood of some success in affecting practice patterns through educational, utilization review, and reimbursement-oriented strategies, these forecasts ultimately may overestimate future cesarean section rates.

The observed trends in obstetric practice patterns are unlikely to have been uniform across individual physicians or hospitals. Cross-sectional data suggest that cesarean section rates vary considerably on the basis of nonclinical patient and organizational factors.[16-18] By extension, different settings of hospital care may have experienced different time trends in cesarean section use. Past research, for example, indicates smaller increases in the cesarean section rate for teaching hospitals than in other settings.[19]

The projection of a 34% cesarean section rate by the year 2000 has substantial policy implications. Hospital and physician charges for cesarean sections ($5,300) are 83% higher than charges for vaginal deliveries ($2,900).[20,21] Therefore, the 36% increase in cesarean section rates projected for 1987 to 2000 will alone raise the cost of obstetric care by 6%. The magnitude of this projected increase should give further impetus to strategies aimed at reducing cesarean section use.

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To Strike or Not to Strike?

House-Staff Attitudes and Behaviors During a Hospital Work Action

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Work actions by house staff are an infrequent response to sometimes difficult working conditions, but they can have a notable effect on institutional cohesiveness and represent a challenge to traditional notions of medical ethics. To determine the extent of participation in a hospital-wide doctors' strike and factors associated with participation, we surveyed 432 house officers at a university-affiliated public hospital where a contract dispute had recently led to a 4-day work action. Of 257 respondents, 69% approved of the strike and 50% participated in it. Both strikers and nonstrikers agreed that quality of care and specific contract issues were important precipitants of the event. By logistic regression, factors independently associated with strike participation ($P<.05$) included being unmarried, training in internal medicine or psychiatry, being in earlier stages of training, being assigned to an outpatient service at the time of the strike, holding a favorable view of physician activism, and perceiving nurses, faculty, peers, and the public to have favored the strike. These associations may provide a basis for understanding the individual and social determinants of house-staff strike activity.

(Kravitz RL, Linn L, Tennant N, Adkins E, Zawacki B: To strike or not to strike? House-staff attitudes and behaviors during a hospital work action. West J Med 1990 Nov; 153:515-519)

Strikes and work actions by practicing physicians are occurring with increasing frequency worldwide,[1-3] but in the United States most strikes have been conducted by physicians-in-training. These events may serve a useful purpose by drawing attention to problems within training centers, but they also have the potential for exacerbating institutional tensions and producing adverse health outcomes. Understanding the genesis of these affairs may have implications for improving organizational effectiveness and for the prevention of future conflicts.

In January 1988, house staff at a large public hospital in the western United States conducted a four-day work action. The event followed a period of protracted negotiations with the county government. County officials had proposed to transfer fiscal and administrative responsibility for the house officers to the affiliated university; house staff argued that such "outcontracting" would damage their ability to bargain collectively and to retain control over discretionary patient care funds. Negotiations intensified, and when the hospital census dropped suddenly as a result of an unrelated nurses' strike, the house-staff organization called for a partial walkout. From January 29 to February 2, physicians marched in picket lines and reduced the amount of nonemergency services they provided. They returned to work when a state superior court judge ordered the county to implement outcontracting on a one-year experimental basis only, during which time the cost-effectiveness of the new arrangements could be evaluated.

Little is known about the factors that influence whether physicians choose to strike. Although strikes by nonphysicians have been studied extensively,[4-6] the conclusions may not apply, as withholding medical services raises complex ethical issues and violates certain professional norms.[7] Two studies of practicing physicians in Canada related participation in a major regional strike to higher income, political conservatism, medical association membership, and professional dissatisfaction.[8,9] No work, however, has examined the factors associated with participation in strikes and work slowdowns by US house staff.

In this study we addressed four questions. First, what was the magnitude of participation in the strike* among house staff in four specialties, and to what degree did "participants" actually withhold services from patients? Second, what were the major precipitants of the strike as perceived by house staff? Third, to what degree did approval of the strike correlate with participation in it? Fourth, what demographic, professional, and attitudinal characteristics were associated with approval of the strike, self-reported strike participation, and a high-level commitment to the strike?

Subjects and Methods

Although the study was conceived shortly after the work action occurred, the principal investigators spent several months negotiating the scope and content of the study with hospital management and with union officials. After gaining final approval in the spring of 1988, we mailed questionnaires to all 457 interns, residents, and fellows training at the facility in internal medicine, surgery, obstetrics-gynecology, and psychiatry. Because of resource constraints, we were unable to sample all clinical departments, but those chosen fielded the four largest training programs at the facility. Interns who were training in internal medicine for one year in preparation for training in other specialties—transitional interns—could not be distinguished from those who planned to complete the three-year program. Because of the sensitivity of the issues and in

*Although the word "strike" implies a more complete withholding of services than "job slowdown" or "work action," in this article the terms will be used more or less interchangeably.

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deference to hospital and union concerns, all questionnaires were strictly anonymous. Although subjects were provided with a precoded postcard for return under separate cover, inconsistent compliance made it impossible to determine exactly who had responded. A $2 payment was included with the initial mailing, and follow-up procedures included two letters and a phone call. After eliminating 25 subjects who were on vacation or on outside rotations during the strike, 257 usable responses were obtained (net response rate, 60%). (Because the various clinical departments could not or would not confirm the accuracy of the master mailing list, this figure represents a lower limit for the true net response rate.) Physicians training in internal medicine and psychiatry responded at a higher rate than those in surgery and gynecology (62% versus 47%), but respondents and nonrespondents did not differ by gender.

Instrument and Scales

Strike attitudes and behaviors were measured by asking subjects whether they approved of the strike (5 = strongly approved, 1 = strongly disapproved), whether they had participated in it, and whether their behavior was consistent with their preferences (1 = participated and wanted to, 2 = participated but did not want to, 3 = did not participate but wanted to, 4 = did not participate and did not want to). Subjects were also asked to estimate the percentage by which they actually reduced their working hours and to specify what strike-related activities they had participated in, if any. They were considered to have reduced their working hours "substantially" if the percent reduction was at least 25%.

Each house officer was asked to rate on a one-to-five scale the importance of six possible underlying causes of the work action: low salaries, heavy workloads, patient overcrowding, poor working conditions, difficulties in providing good quality of patient care, and contracting out of services by the county to the university. These six issues were generated through discussions with house staff, faculty, nurses, and hospital management. Space was provided for house staff to make additional comments.

With respect to factors possibly associated with striking, subjects were questioned about demographic and professional background (age, race, sex, marital status, level of educational debt, specialty, level of training), attitudes (position on the political spectrum, view of physician activism, religiosity), degree of perceived support by significant others, job satisfaction, and barriers to participation (assignment to the wards or intensive care unit at time of strike).

Demographic and professional characteristics were queried in a standard manner. Position on the political spectrum was rated on a five-point scale (5 = conservative, 1 = liberal). The view of physician activism was measured by summing the number of activities subjects deemed "proper" for physicians to participate in (placing "activist" pamphlets or posters in wards or clinics, wearing buttons with activist slogans while on duty, participating as physicians in marches or other demonstrations, and joining unions). Scores on this scale ranged from 0 to 4. Religiosity was rated from extremely religious (5) to not at all religious (1). Degree of perceived support for the work action was measured by counting up the number of persons or groups perceived to have "approved" or "strongly approved" of the strike (most of the residents you work with, most of the nurses you work with, most of the attending faculty in your specialty, the general public; range, 0 to 4). Job satisfaction was computed as the mean of two items: How would you rate your overall satisfaction with your experience as a house officer at this institution (5 = extremely satisfied, 1 = very dissatisfied)? and Would you recommend this institution to applicants as a place to train in your specialty (5 = definitely yes, 1 = definitely not)? For the purpose of analysis, house officers with job satisfaction scale scores above the mean were considered to have "high satisfaction"; all others were considered to have "low."

Subjects failing to complete any item in a scale were considered missing with respect to that scale. Cronbach α-reliability coefficients for all multi-item scales ranged from 0.60 to 0.85.

Statistical Analysis

Strike approval and participation rates were determined first for the entire sample and then among demographic, professional, and attitudinal subgroups; differences were assessed by computing χ^2 and Mantel-Haenszel χ statistics as indicated using the SAS statistical package.[10] To determine the strength of independent associations between subject characteristics and strike approval, strike participation, and "substantial" hourly reductions, variables significant in the bivariate analyses were entered into three fixed multivariate regression models. The first model used multivariate linear regression to explain the variance in strike approval (1 to 5 scale). The second and third models used multivariate logistic regression to compute the odds of subjects having participated in the strike (1 = yes, 0 = no) and having reduced their work hours substantially (1 = $\geq$25% reduction, 0 = $<$25% reduction). (See Table 3 for specification of independent variables.)

Results

Of 257 respondents, 69% "strongly" or "somewhat" approved of the strike (Table 1). Rates of approval were highest among psychiatrists and lowest among surgeons. Approval of the strike did not automatically imply participation: of those who approved, 63% participated in the strike compared with 10% of those who disapproved or who were uncertain (data not shown). Of those who approved, 29% cut their work hours by at least 25% compared with none of those who did not approve.

TABLE 1.—*Strike Approval and Strike Participation*

	Strike Approval		Strike Participation			
Physician Respondents	*Approved, No. (%)*	*Disapproved or Uncertain, No. (%)*	*Participated; Wanted to, No. (%)*	*Participated; Did Not Want to, No. (%)*	*Did Not Participate; Wanted to, No. (%)*	*Did Not Participate; Did Not Want to, No. (%)*
All subjects	175 (69)	79 (31)	102 (40)	24 (10)	48 (19)	79 (31)
Internal medicine	87 (69)	39 (31)	53 (42)	14 (11)	22 (17)	38 (30)
Surgery	19 (45)	23 (55)	4 (9)	3 (7)	8 (19)	28 (65)
Obstetrics-gynecology	20 (77)	6 (23)	4 (15)	0 (0)	13 (50)	9 (35)
Psychiatry	49 (86)	8 (14)	41 (72)	7 (12)	5 (9)	4 (7)

The overall strike participation rate was 50%, but withdrawal of services was incomplete: less than 1% of striking subjects stopped answering their pages, and only 26% of strikers reduced their working hours by more than half (median 25%, range 0% to 100%). Other behaviors reported by strike participants included helping to organize the strike (20% of strikers), speaking out in favor of the strike (66%), and marching in picket lines (82%).

Most subjects considered the conflict to have been precipitated by several issues: difficulties in providing good quality of care (86%), the county's plan to turn house-staff contracts over to the university (80%), patient overcrowding (78%), poor working conditions (74%), and heavy workloads (56%). Only 11% thought that salary was an "extremely important" or "very important" issue. Work action participants and nonparticipants generally shared the same views about the underlying causes of the event. House staff who supported the strike, however (regardless of behavior), were more likely to report concerns about quality of care as having been important (91% versus 78%, $P<.01$).

Of 126 strike participants, 24 (19%) reported that they "did not really want to participate" (Table 1). Conversely, of 127 nonparticipants, 48 (38%) said that they had "really wanted to participate." The discordance between attitudes and action was particularly pronounced for the 26 trainees in obstetrics-gynecology, among whom 50% "did not participate in the strike but really wanted to." The corresponding percentages for other specialties ranged from 9% (psychiatry) to 19% (surgery) (Table 1). Among all participants, 65% said that they would strike again under similar circumstances.

In the bivariate analysis, nonfellows, trainees in internal medicine or psychiatry, and those with a greater educational debt were more likely than their peers to register strong approval of the strike (Table 2). Physicians assigned to outpatient or consultative services during the month of the work action were also more likely to approve of it. Attitudes associated with greater strike approval included more liberal politics, lower job satisfaction, greater perceptions of support for the strike, and more frequent endorsement of physician activism (Table 2).

Variables related to strike approval were uniformly associated with strike participation, substantial reductions in working hours, or both. Younger age, minority race, and being unmarried were associated with strike participation but not approval (Table 2).

In the multivariate analysis we determined the independent association of ten demographic, professional, and attitudinal characteristics with strike approval, self-reported strike participation, and substantial reduction of working hours (Table 3). Strike approval was related to minority race, liberal politics, stronger endorsement of physician activism, and more frequent perceptions of support for the strike (multiple R^2, 0.33). Strike participation was also associated with greater activism and perceptions of support but, in addition, was related to being unmarried, being a nonfellow, working on an outpatient or consultative service during the strike, and training in internal medicine or psychiatry. The model correctly classified subjects as strikers or nonstrikers 79% of the time. Curtailing customary working hours by at least 25% was independently associated with being a nonfellow, working on an outpatient or consultative service, training in medicine or psychiatry, and holding a liberal position on the political spectrum. Neither strike approval nor behavior was related to job satisfaction.

Discussion

Much of the care provided to medically indigent persons in public hospitals is delivered by physicians-in-training, often under demanding conditions.[11] It is not surprising that these physicians have periodically organized in defense of their interests and those of their patients. Nevertheless,

TABLE 2.—*Approval and Participation in the Strike Among Subgroups of Physicians (n=257)**

Characteristic	*Percent Strongly Approved*	*Percent Partici-pated*	*Percent Substantially Reduced Hours*
Age, years			
Younger than 29 (n=72)	46	61	28
29 to 32 (n=124)	44	45	13
Older than 32 (n=61)	45	43†	22
Level of training			
Intern (n=29)	52	59	18
Resident (n=149)	49	59	30
Fellow (n=78)	32†	27‡	5‡
Work area time of strike			
Ward (n=178)	46	48	19
Intensive care unit (n=22)	18	32	0
Clinic or consult service (n=53)	52†	64†	38‡
Specialty			
Surgery or gynecology (n=69)	34	16	1
Internal medicine or psychiatry (n=184)	49†	62‡	29‡
Gender			
Male (n=192)	42	49	19
Female (n=62)	52	50	27
Marital status			
Married (n=126)	42	49	15
Not married (n=127)	47	58§	26
Race			
White (n=171)	42	45	18
Other (n=83)	49	59†	26
Family income			
>$45,000 (n=97)	46	48	21
≤$45,000 (n=157)	43	50	21
Level of educational debt			
>$30,000 (n=103)	59	59	24
≤$30,000 (n=150)	35‡	43§	19
Religiosity			
At least somewhat religious (n=138)	42	50	20
Not very or not-at-all religious (n=116)	47	48	22
Position on political spectrum			
Liberal (n=99)	57	58	32
Moderate (n=65)	43	55	20
Conservative (n=89)	33‡	36§	8‡
Job satisfaction			
High (n=131)	37	44	14
Low (n=123)	53†	55†	28§
Number of significant groups perceived to support strike			
0 to 1 (n=44)	14	20	12
2 (n=112)	44	45	17
3 to 4 (n=97)	58‡	68‡	29‡
Number of "activist" activities deemed proper			
0 to 1 (n=58)	16	24	7
2 to 3 (n=111)	44	50	22
4 (n=85)	65‡	66‡	28‡

*Total number of respondents differs for each characteristic because some respondents did not answer all of the questions.
†$P<.05$.
‡$P<.001$.
§$P<.01$.

for a physician to go on strike means at least a temporary retreat from the traditional Hippocratic notions of beneficence.[12] For house officers as for other workers, strikes and work actions occupy one end of a continuum that includes dialogue, negotiation, and coercion. The decision of an individual physician to strike is complex, involving questions of necessity, ethics, and personal risk. Because of the cross-sectional and retrospective nature of this study, associations do not imply causation. Our results, however, are consistent with the hypothesis that house officers at one institution decided whether or not to strike based partly on a combination of background characteristics; perceptions of peer, nurse, faculty, and public support; political attitudes; and the perceived absence of practical barriers. With few exceptions, the findings are in accord with studies of nonphysicians that have related strike participation (specifically) and high-risk activism (generally) to these same four elements.[5,6,13]

We found that although approval of the strike among respondents was widespread, house officers in our sample were generally reluctant to withdraw services in a manner that would significantly impair the delivery of patient care, even though such behavior would have provided a more effective lever on the hospital administration. Strike participants continued to respond to their pages, and relatively few shortened their workday by a substantial margin.

TABLE 3.—*Multivariate Regression of Strike Approval, Strike Participation, and Service Withdrawal as a Function of Demographic, Professional, and Attitudinal Characteristics*

Characteristic	β-Coefficient (Standard Error)*		
	Degree of Approval	Reported Strike Participation	Substantial Reduction of Working Hours
Minority race	0.46 (0.16)†	0.46 (0.36)	0.34 (0.43)
Married	−0.20 (0.15)	−0.71 (0.33)‡	−0.31 (0.41)
Fellow (v intern or resident)	−0.20 (0.17)	−1.61 (0.39)§	−2.62 (0.67)§
Outpatient or consult service at time of strike	0.23 (0.18)	0.95 (0.42)†	1.71 (0.50)‖
Surgical or gynecologic specialty	0.12 (0.19)	−1.88 (0.44)§	−3.00 (1.08)‖
High educational indebtedness (>$30,000)	0.24 (0.15)	0.40 (0.34)	−0.02 (0.42)
Liberal politics (v moderate or conservative)	0.20 (0.09)‡	0.29 (0.39)	1.46 (0.53)‖
Number of activist activities deemed proper (0 to 4 scale)	0.30 (0.06)§	0.30 (0.14)‡	0.001 (0.18)
Job satisfaction below mean	0.25 (0.15)	0.33 (0.34)	0.49 (0.43)
Number of groups perceived to favor strike (0 to 4 scale)	0.35 (0.09)‖	0.52 (0.21)†	0.14 (0.24)
Multiple R^2	0.33	..	..
Percent of cases correctly classified, %	..	79	83

*Reported coefficients are obtained from multivariate linear regression analysis (strike approval) and from multivariate logistic regression analysis (strike participation and reduction in working hours by at least 25%).
†$P<.01$.
‡$P<.05$.
§$P<.0001$.
‖$P<.001$.

Whether cognizant of their critical value to patients or fearful of repercussions from superiors, none of the 22 physicians assigned to the intensive care units during the strike curtailed their working hours by more than 25%.

That some house staff approved of the strike yet did not participate and others disapproved and participated probably reflects serious ambivalence about the wisdom and propriety of striking. The findings argue indirectly for the importance of perceived risk (in the case of those who wanted to strike but did not) and peer pressure (in the case of those who did not want to strike but did). An alternative explanation is that some subjects in this retrospective survey revised their expressed opinions to coincide with their perceptions of the outcome.

Specialty, level of training, and work assignment were consistently related to strike behavior. Though not a part of the formal study, interviews with house staff and administrators revealed that program directors in surgery and gynecology displayed greater antagonism towards the strike than did directors in medicine and psychiatry. Fellows may have been less likely to strike because they thought they had more to lose as a result of participating in an activity condemned by their superiors, because they had less stake in the issues, or because they tended to identify more with the views of the administration and faculty than with those of less advanced trainees. Finally, house staff assigned to the wards and intensive care units may simply have been less "biographically available"[13] for participation in strike activities. Increased clinical demands may have also been a factor in explaining why surgery and gynecology house staff were less likely to strike.

Studies of activism in other settings have documented the importance of ideologic commitment and perceived norms.[13,14] Strike participants in our study had liberal political views and were more concerned than nonparticipants about problems with quality of care at the medical center. They were also more likely to perceive co-workers, attending physicians, and the public to have favored the work action. Although their perceptions may have been biased, these findings suggest that house staff may have struck partly out of deference, loyalty, or fear of ostracism by significant others.

Approval of the strike was largely related to political attitudes and perceptions of peer support. In contrast, the strongest independent correlates of strike behavior were level of training, specialty, and work assignment at the time of the strike. Evidently, what house officers *did* was much more constrained by the practical conditions of their professional lives than what they *thought*.

Surgeons and gynecologists were less likely to respond to the survey than trainees in internal medicine and psychiatry. If the behavior of respondents in surgery and gynecology was representative of the behavior of nonrespondents, the overall strike participation rate reported in this study was probably inflated. The main results were robust enough to withstand considerable response bias, however. For example, even if two thirds of nonresponding surgeons and gynecologists participated in the strike and two thirds of nonresponding internists and psychiatrists did not, the strike participation rate difference would still favor internists and psychiatrists by 4%.

The work action reported here was promoted by circumstances unique to the medical center where it occurred. In addition, the study was limited to selected specialties. Nevertheless, similar social dynamics may be generalizable to house staff in other hospitals, particularly because the pat-

terns are consistent with accepted theory and existing empiric data.[9,13]

Physicians' strikes and work slowdowns may be an important sign of serious trouble with patient care or professional morale. They are, however, a late sign, and they can potentially impose serious morbidity on patients. This study shows that house staff can probably be deterred from participating in strikes by strong social pressure and by a reliance on their reluctance to endanger patients. If the underlying sources of discontent are not addressed, however, patient care may suffer in other ways. The strike in the present case may indeed have been unavoidable, but more conspicuous efforts by county and university officials to listen and respond to house-staff concerns might have helped to avert an incident that in the end engendered much bitterness and accomplished little.

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Commentary

Peer Review in Scientific Journals—What Good Is It?

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Presented at the Plenary Session, Western Association of Physicians, Carmel, California, February 6, 1990, as the association's Distinguished Lecture.

Recent concerns about the publication of fraudulent or shoddy science and about economic conflicts of interest and other biases of authors and reviewers have focused much interest on the peer review process and raised questions about its value, reliability, and objectivity. Two major conferences on peer review have been held within recent years. In October 1988 in Washington, DC, the Council of Biology Editors organized a conference on this subject. Then in May 1989, the American Medical Association sponsored an International Conference on Peer Review. On both of these occasions, concern was expressed about the quality and reliability of peer review. Peer review was criticized for not being more effective in ensuring the validity and honesty of published work. Questions were raised about whether it is an unscientific, subjective, and arbitrary process, even whether it is simply an unnecessary impediment to the communication of information. In short, the critics were asking, "What good is peer review?"

Before we can answer that question, we need to have a clear understanding of exactly what peer review is. Up until now it has been regarded as a kind of confidential transaction, much misunderstood, even by scientists. First I will describe what is done at the *New England Journal of Medicine* as a background for trying to answer questions about the value and usefulness of the process.

Original scientific contributions constitute roughly two thirds of all the articles submitted to the *New England Journal of Medicine*. We receive each year approximately 2,500 such communications. They are logged into the computerized system and sent to the editor's desk, where an initial screening eliminates roughly 10% of the manuscripts as being obviously unsuitable for us. The remaining 90% are assigned to associate editors and sent out for review. Initially at least two referees are chosen by the associate editor from a large list of experts in every field. In reviewing the manuscript, the referees offer specific technical comments and criticisms that will ultimately be transmitted to the author and a confidential overall assessment that goes to the editors only. When the reviews come back from the referees, they are assessed and the manuscript is read again by the associate editor. Each of the five associate editors is required to bring to our weekly editorial meeting for further consideration at least the three best reviewed manuscripts that he or she has received back from review that week. Thus, each week we discuss at least 15 scientific manuscripts or about 30% of the total received. After discussion, about 6 or 7 are kept alive for further review and revision. Every paper that is considered a possibility goes through statistical review if it has any kind of quantitative data.

Ultimately, about 250 scientific manuscripts each year, or about 10% of the original 2,500, survive the process and are published. The total elapsed time between initial receipt and final acceptance averages about three to four months, but there is a wide variance. The fastest that we have ever processed a scientific manuscript from receipt to final acceptance is about 2½ or 3 weeks and the longest well over a year. During this time the manuscript will have been through one to three revisions and will have been seen by two to six referees, plus an associate editor, a deputy editor, and, finally, the executive editor and me. After acceptance, the paper is published in about seven weeks.

Should referees be required to identify themselves to the author? This issue has been widely discussed. The concern is that unidentified, nameless referees are more likely to offer harsh, unjustified, or irresponsible criticism. We do not worry about that; if a review is abusive and not constructive, we will not transmit it. We think anonymity encourages frank and rigorous criticism. If reviewers were forced to sign their reviews, papers submitted by distingushed, influential, or powerful people would probably get different treatment from those submitted by relatively junior investigators. Papers submitted by friends, relatives, and patrons of the reviewer would get different treatment from papers submitted by others. So we leave the choice of signing up to the referee, and about 85% of the time, the referee chooses not to sign. We think that is the best way to do it.

Would the quality of reviewing be improved by blinding the referee to the identity of the author? Some argue that a referee who does not know who is submitting the paper being reviewed would be less biased and more likely to consider it purely on its merits. I think that if blinding could be done easily and reliably most of the time, there would be no harm in trying, but I am not convinced that it would make much difference. The structure of a paper frequently contains clues to its origin. Some experiments are being done now to see how often reviewers can be blinded and with what effect. To the best of my knowledge, the results so far are not impressive or convincing.

The problem of referee bias remains a source of concern, however. The referee may be a scientific rival or, alternatively, a scientific ally of the author and therefore may be biased for or against a paper's conclusions. The referee may have an economic conflict of interest. Some editors now require reviewers to reveal all potential conflicts of interest, with the implication that reviewers may be disqualified on such grounds. I find that difficult to understand. Anyone who is really an expert in a field has almost certainly pub-

(Relman AS: Peer review in scientific journals—What good is it? West J Med 1990 Nov; 153:520-522)

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These remarks are based on earlier comment by Relman and Angell in the *New Englond Journol of Medicine*.

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lished on the same subject and has taken some sort of scientific position that might theoretically be considered a kind of bias. More and more reviewers, particularly in molecular biology, are likely to have some economic involvement in the area. In my opinion, this does not matter; the final decision should not be made by the referees. Referees are consultants, not arbiters of publishability. Peer review is not a straw vote among referees but rather a source of information and technical advice to the editors, who should make the final decision. The editors consider the opinions of several people, not just one referee, and it is the editors' responsibility to weigh the possibility of bias in the advice they receive. On the other hand, we *are* concerned about economic conflicts of interest involving authors. Whereas we do not ask referees to disclose economic conflicts of interest, we do expect authors of original scientific articles to provide such data. That information is not shared with the reviewers because we want the review process to be concerned primarily with the scientific merits of the paper. Economic ties are disclosed when we publish the paper, however, because once the science has passed peer review, full disclosure is essential.

In reviews, editorials, and other opinion pieces, readers do not have the data on which the conclusions are based and must depend on the judgment of the author in selecting and interpreting the literature. In these circumstances, where economic conflicts of interest pose a more serious problem, we have decided that disclosure is not enough. Henceforth we will not consider a scientific review article or opinion piece written by anyone with a substantial economic conflict of interest. We will no longer accept a review article or an editorial on a scientific subject written by someone who holds equity interest, is on the scientific advisory committee, is a paid consultant, or is an employee of a corporation selling products relevant to the topic under discussion.

The role of the editor as moderator of the review process is crucial. Editors weigh the advice they receive; they do not simply record and transmit it. They edit the transmitted comments, they may add some comments of their own, and they are responsible for reconciling differences among the referees' comments and clarifying ambiguities. Our editors do not require unanimity among referees to reach a decision. We may even go against the general advice of our referees. We rarely, if ever, go against their technical or scientific judgments, at least not without resolving the issue by further consultation with other experts. But often referees will base their final advice on whether they like the manuscript's style, or whether they think the paper is suitable for our readers, or whether they find it interesting. We pay close attention to these opinions, but there is often disagreement among referees on such matters, and, in any case, we think the final decision should rest with the editors. We rely on our reviewers to tell us whether an article is an original, scientifically significant piece of work, whether the design of the experiment and the methods are sound, and whether the analysis stands up to criticism. But we also select articles on the basis of their general interest, readability, and relevance for our readership and our kind of journal. Balance and mix of journal content are also important editorial considerations. If we wanted to, for example, we could become the "Journal of AIDS," based on the huge number of submitted manuscripts on the topic. We recently received many papers on the syndrome of eosinophilic fasciitis due to tryptophan ingestion. Not being able to publish them all, we had to select only a few to maintain an appropriate balance of subject matter. Such decisions about interest and suitability, relevance, readability, and balance are editorial decisions that cannot be left to the reviewers.

Rejected authors have a right to appeal and rereview if our editorial decision has been based largely on scientific and technical considerations. If authors claim the reviewers were wrong, or did not understand the paper, or if they say they can deal with the scientific criticisms, we will usually offer a second review, although a reversal of our decision would require a clear resolution of the scientific issues in the authors' favor. If we have rejected a paper on the basis of more general editorial concerns, however, we are not likely to reconsider.

The peer review process that I have described is expensive and time-consuming. I estimate conservatively that we spend in-house about $1 million a year on peer review. In addition, about 15,000 to 20,000 hours of voluntary referee effort is required. If the time of these biomedical experts is arbitrarily estimated to be worth $100 per hour, that would be another $1½ to $2 million. What do we get for all that effort and money?

Peer review cannot guarantee the validity or the ultimate truthfulness of a work. Peer review is fallible; no human enterprise is entirely free of error. The process can occasionally miss honest mistakes and overlook observer bias. Most of all, we have to realize that science is constantly changing. New methods and new concepts can invalidate even the most carefully reviewed work that was free of detectable error at the time it was published. Much scientific error becomes apparent only in retrospect as a field advances. In a sense, science advances by the continual discovery and correction of past error. Error is an essential part of science. We know that a considerable fraction of the material published today, even in the best peer-reviewed journals, will ultimately be found to be at least partly in error.

The peer review process cannot be relied on to detect and rule out fraud. The reason is very simple. Discourse among scientists must be based on a kind of trust. When scientists say, in effect, "This is what we did, and this is what we observed," we have to believe them. The peer review process challenges the soundness of the design, the appropriateness of the methods, the quality of the evidence, the interpretation and analysis, and the conclusions. But if we cannot assume that the authors honestly described what they did and what they observed, then any further discourse is impossible. We cannot monitor the experiments being done; we cannot have a policeman in the laboratory, nor can we ask our colleagues to submit sworn affidavits that they have not lied to us. There must be an assumption of trust, and if scientists have lied about their work, we probably would not know it unless we were there to see what they did. If the fraudulent results are plausible, internally consistent, and not too startling, they usually are not detected by peer review. The fabrication has to be clumsy, careless, or incredible to be recognized or suspected during the review of a manuscript.

Fraud is best prevented by having scientists working in a collegial atmosphere where their work is open to inspection by co-workers and supervisors. Fraud is almost always the work of individuals, not a team. Usually one misguided, unhappy person is driven to lie for some reason or other, and if that person works alone without supervision, the lie may not be immediately detected. Another good way to prevent fraud is to see that there are institutional mechanisms for the supervision of young people and for the sharing of data. Senior scientists who take responsibility for the adminis-

tration of research grants also must take responsibility for the gathering of the data and the monitoring of everything going on in their laboratories. Close supervision by directors of research units is essential.

I do not agree at all with those who urge that journals should establish some kind of random auditing system or require the submission of raw data. It would be a waste of time, and it would be counterproductive. A lie can be transmitted within data books as well as within a submitted manuscript. Inspection would chill the atmosphere by generating suspicion and distrust. Science cannot flourish under such conditions.

I am opposed to journals trying to ferret out fraud by conducting audits or investigations. On the other hand, when a serious suspicion of fraud is raised by reviewers or someone close to the work, an editor has the responsibility to see that the institution from which the work originated is apprised of that suspicion and investigates the allegations in an appropriate way.

If peer review is expensive and time-consuming, subjective and fallible, and if it cannot guarantee validity or reliably detect fraud, what good is it? What does peer review really accomplish?

First of all, peer review enables each individual journal, with its own character and its own special focus and interest, to select the work that is best and most suitable for it. Journals need to be predictably diverse; otherwise there would be a vast, homogenized literature that could be used only through a computerized search. That would be impractical, if not impossible. We have to be able to go to a relatively few journals in our field to find most of the information we want. The peer review process results in a sorting out of material among the various journals, thus allowing us to read the literature efficiently.

Second, peer review holds manuscripts to the highest current standards. Knowing that their manuscript must pass rigorous peer review, most authors will do the best they can. If there were no peer review and journals simply published whatever was sent, we would quickly be awash in a sea of mediocrity and background noise; reports of good science would be swallowed up by a vast amount of shoddy work. The existence of peer review tells authors that if they want to get their work published in the journals that are read most widely and are most trusted, they will have to submit good work. Even so, much shoddy work is submitted for publication, and another important role of peer review is to screen out the obviously flawed and invalid manuscripts. This it can do fairly reliably.

Peer review improves the quality of manuscripts that are published by requiring revisions, more data, reanalysis, and so on. Peer review also improves the readability of what is published. Biomedical science is in danger of splintering apart because of the arcane, specialized language used in each new field. Scientific progress requires interactions; advances in science require not only digging deeply into one narrow field but making connections with work going on in other fields. That is facilitated by having interesting and important new developments written in clear, concise, relatively simple language that can be read and understood by many scientists and physicians. This kind of clarity is important not only for other investigators, but particularly so for physicians in practice if they are to be able to understand the latest developments in biomedical science and their application to human health.

Peer review necessarily concerns itself with quality, which is easier to recognize than to measure. Judgments of quality can never be totally objective or quantitative. Many of the defects in quality control are due to inadequate editorial supervision, and quality certainly could be improved by better, more conscientious, and more expeditious editing. For many peer review journals, the part-time editor is busy with other duties, does not have an adequate in-house staff, and cannot spend enough time at the editorial desk. This may lead to an almost total reliance on the opinions of referees. Referees are absolutely essential for technical evaluation, but the editor must moderate and monitor the process in many ways, and part-time editors often have a difficult job doing that. More full-time editors and a greater attention to editorial responsibilities can improve the process.

Even at its best, the peer review process has inherent limitations, all of which I have tried to make clear. Despite its limitations, we need it. It is all we have, and it is hard to imagine how we could get along without it.

Conferences and Reviews

Chlamydial Infections

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Chlamydiae are among the most common human bacterial pathogens. *Chlamydia trachomatis* has long been known as the causative agent of trachoma, the world's leading cause of preventable blindness.[1] Only in the past two decades have we realized that this organism is an important cause of genital tract disease. These infections are important not only because of their incidence but also because the infections result in long-term consequences such as tubal factor infertility and ectopic pregnancy. *C psittaci* is recognized as the cause of psittacosis, a relatively uncommon human infection acquired through exposure to infected birds. In recent years what was thought to be a variant of *C psittaci*, with no known avian reservoir, was recognized as a cause of atypical pneumonia in humans. This variant, originally called the TWAR agent, has now been placed in its own species. It, too, has been found to be a very common human pathogen. Both the clinical manifestations and epidemiology of this infection are currently being researched.

Taxonomy

The chlamydiae are among the more common pathogens throughout the animal kingdom. They are nonmotile, gram-negative, obligate intracellular bacteria. Their unique developmental cycle differentiates them from all other microorganisms.[2] They replicate within the cytoplasm of host cells, forming characteristic intracellular inclusions which can be seen by light microscopy (Figure 1). They differ from the viruses by possessing both RNA and DNA and cell walls quite similar in structure to those of gram-negative bacteria. They are susceptible to many broad-spectrum antibiotics, possess a number of enzymes, and have a restricted metabolic capacity. None of these metabolic reactions results in the production of energy. Thus, they have been considered as energy parasites that use the ATP produced by the host cell for their own requirements.

Chlamydiae are presently placed in their own order, the Chlamydiales, family Chlamydiaceae, with one genus, *Chlamydia*.[2] There are three species, *C trachomatis, C psittaci*, and *C pneumoniae*.[3] *C trachomatis* includes the organisms causing trachoma, inclusion conjunctivitis, lymphogranuloma venereum (LGV), and genital tract diseases (Table 1). There are three biovars within the species: the trachoma biovar, the LGV biovar, and the murine biovar. *C trachomatis* strains are sensitive to the action of sulfonamides and produce a glycogen-like material within the inclusion vacuole, which stains with iodine. *C psittaci* strains infect many avian species and mammals, producing the diseases psittacosis, ornithosis, feline pneumonitis, bovine abortion, and so on.[4,5] They are resistant to the action of sulfonamides and produce inclusions that do not stain with iodine. *C pneumoniae*, the most recently described species, has the same sulfonamide sensitivity and iodine staining characteristics as *C psittaci*. However, it has less than 10% DNA relatedness to the other species and has pear-shaped elementary bodies rather than round ones. It appears to be exclusively a human pathogen. *C pneumoniae* has been identified as the cause of a variety of respiratory tract diseases and has worldwide distribution.

Growth Cycle

Following attachment at specific sites on the surface of the cell, the elementary body (EB) enters the cell in an endosome in which the entire growth cycle is completed. Chlamydiae are ingested by susceptible host cells through a mechanism similar to receptor mediated endocytosis.[6] The uptake process is directly influenced by the chlamydiae, and ingestion of organisms is specifically enhanced.[7] The chlamydiae prevent phagolysosomal fusion. Once the EB (diameter, 0.25 to 0.35 μm) has entered the cell, it reorganizes into a reticulate particle (RB or initial body), which is larger (0.5 to 1 μm) and richer in RNA. After approximately eight hours, the RB begins dividing by binary fission. Approximately 18 to 24 hours after infection, some of the RBs become EBs by a poorly understood reorganization or condensation process (Figure 2). The EBs are then released to initiate another cycle of infection. The EBs are specifically adapted for extracellular survival and are the infectious form. In contrast, the intracellular, metabolically active, and replicating form, the RB, does not survive well outside the host cell and seems adapted for the intracellular milieu.

The chlamydiae appear to have evolved a unique structure consistent with the requirements of this growth cycle. Structural rigidity of the EB is not maintained by a peptidoglycan layer as is typical for bacteria. The rigidity of chlamydiae is based on cross-linking of three cysteine-rich proteins.[8] The most important of these is the major outer membrane protein (MOMP), which makes up 60% of the weight of the outer membrane.[9] MOMP is about 40 to 45 Kd in mass and contains serovar- and species-specific antigens.[10] In the EB, MOMP is bound to other MOMP molecules and to proteins of approximately 15 and 60 Kd by disulphide bonds. When reduced, MOMP forms porins, channels to allow entry of nutrients.[11] The more flexible outer membrane of the intracellular and metabolically active RB seems to be the reduced form.

History

Chlamydia trachomatis

Trachoma, one of the oldest recognized human diseases, was described in Egyptian papyri and in ancient Chinese writings.[1] The causative agent, *C trachomatis*, was first seen in stained conjunctival scrapings (see Figure 1). The diag-

(Schachter J: Chlamydial infections. West J Med 1990 Nov; 153:523-534)

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This work has been previously published as an update to the CECIL TEXTBOOK OF MEDICINE, WB Saunders, Philadelphia, and sponsored by Key Pharmaceuticals, makers of NORMODYNE (labetalol HCl) tablets.

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nostic intracytoplasmic inclusions were found first in specimens from experimentally infected nonhuman primates and then from humans. Shortly thereafter, the neonatal form of *C trachomatis* conjunctivitis (inclusion conjunctivitis of the newborn [ICN] or inclusion blennorrhea) and the related genital tract infections were recognized. For 50 years laboratory diagnosis was restricted to the search for inclusions in Giemsa-stained epithelial cell scrapings (see Figure 1). The agent was not isolated until 1957, when Chinese workers recovered the organism by inoculating conjunctival scrapings from trachoma patients into the yolk sac of embryonated hens' eggs.[12] Interest in *C trachomatis* grew with increased awareness of its role in genital tract disease.[13,14] Improved laboratory methodology—particularly tissue culture isolation procedures and the valuable epidemiologic tool of the microimmunofluorescence (micro-IF) test for measuring antibodies to *C trachomatis*—led to the elucidation of the wide clinical spectrum of this organism.[15,16] The most important revelation was the etiologic role of *C trachomatis* in acute salpingitis.[17] In many areas this is now recognized as the leading cause of pelvic inflammatory disease and the long-term consequences of tubal factor infertility and ectopic pregnancy.

In 1975, during a prospective study of inclusion conjunctivitis of the newborn, it was noted that some of the infants exposed to *C trachomatis* at birth developed pneumonia.[18] A characteristic pneumonia syndrome of infancy was then described and associated with chlamydial infection.[19] *C trachomatis* was quickly recognized as a major cause of pneumonia in the first six months of life.

A more invasive biovar of *C trachomatis* causes the systemic sexually transmitted disease lymphogranuloma venereum (LGV). This condition was first described in the late 1700s and the causative agent isolated in 1929.[1] *C trachomatis* biovars infecting humans have no known animal hosts.

Chlamydia psittaci

Psittacosis was first described in Switzerland in the 1870s.[1] Outbreaks of the disease were reported from a number of countries in Europe and the association with exotic or psittacine birds was recognized. The pandemic of 1929-1930 brought worldwide attention to the disease because of the approximately 20% fatality rates seen in the preantibiotic era. In the 1950s the importance of *C psittaci* infections (ornithosis) in poultry was recognized, and human psittacosis was described as an important occupational hazard to workers in poultry processing plants.[20]

Human psittacosis is a zoonosis, usually contracted from exposure to an infected avian species. *C psittaci* is ubiquitous among avian species. The birds usually have intestinal tract infections. The organism is shed in the feces, contaminates the environment, and is spread by aerosol.

C psittaci is also common in domestic mammals. In some parts of the world these infections have important economic consequences. *C psittaci* is a cause of a number of systemic and debilitating diseases in domestic mammals and, most importantly, can cause abortions.[5] Although human chlamydial infections resulting from exposure to infected domestic mammals are known,[21] they seem to be relatively uncommon.

TABLE 1.—*Natural Host Ranges of Chlamydiae and Human Diseases*

Species	Natural Hosts	Human Diseases
1. *C psittaci*	Birds, lower mammals	Psittacosis
2. *C pneumoniae*	Humans	Respiratory
3. *C trachomatis*		
a. Trachoma biovar	Humans	Trachoma, conjunctivitis, genital diseases, infant pneumonia
b. LGV biovar	Humans	Lymphogranuloma venereum
c. Murine biovar	Mice	None known

Chlamydia pneumoniae

During studies of trachoma performed in Taiwan and Iran, some apparent *C psittaci* strains were recovered from conjunctival swabs. Seroepidemiologic studies have suggested that infections with these strains (then called TWAR) are common in many parts of the world.[22,23] Age-specific prevalence rates suggest that transmission occurs in childhood and peaks early in adult life. *C pneumoniae* appears to be circulating among humans without an avian reservoir. It has been associated with a variety of respiratory diseases.[24]

Epidemiology

The epidemiology of chlamydial infections has some common characteristics. Because of the long growth cycle (48 to 72 hours), incubation periods are relatively long, usually on the order of one to three weeks. Persistent low-grade, clinically inapparent infections are common.

Chlamydia trachomatis

Trachoma. Trachoma is the world's leading cause of preventable blindness.[25] Approximately 600 million people are affected, with 10 million blinded. Trachoma is a major public health problem in many developing countries, particularly those in North Africa, sub-Saharan Africa, and Southeastern Asia. In these settings the infection is holoendemic, with virtually all members of affected communities acquiring the infection before they are two years old. It is a disease of families and of poverty, being found at highest rates and in the most severe form among the poorest segments of society. The prevalence of trachoma responds markedly to improving socioeconomic conditions. It has disappeared from some countries as a result of improved standard of living rather than of specific antitrachoma measures.

Young children with severe inflammatory disease are the main reservoirs for infection. Trachoma is a family disease, typically spread from child to child by direct personal contact. Flies can act as mechanical vectors because they feed on ocular discharges. Occasionally, adults may have active disease or may be inapparent shedders of the agent and therefore a source of infection for some children in the household.

Genital Infection. Genital infections are sexually transmitted. The proportions of society most affected are those at highest risk for other sexually transmitted agents.[13,14,26] Members of lower socioeconomic strata—particularly sexually active teenagers—have the highest prevalence of *C trachomatis* infection.[27] In industrialized societies, *C trachomatis* is now the most common sexually transmitted bacterial pathogen.[28] In the United States more than 3 million new infections are estimated to occur each year. (This may be compared with 1.8 million gonococcal infections and approximately 500,000 genital infections with *Herpesvirus hominis*).[29] Most prevalence and clinical studies have been done in the United States and in western Europe.

Sexually transmitted chlamydial infections appear to be just as important in many developing countries.[30]

Sexually transmitted chlamydial infections are widely distributed among the population. These infections are found at relatively high rates in populations that are at low risk for gonorrhea. For example, in higher socioeconomic groups gonorrhea is seldom encountered but chlamydial infections are common. In these settings, as exemplified by students being screened at private colleges, chlamydial prevalence often exceeds the gonococcal infection rate by a factor of 5- to 10-fold in symptomatic men or in asymptomatic women having routine pelvic examinations.[31] In general, it is only in the urban center venereal disease clinics that chlamydial and gonococcal infections occur at the same rate or in which, perhaps, gonococcal infections may be more common. In screening studies of women attending family planning clinics for birth control advice, chlamydial infection rates often exceed gonococcal recovery rates by a factor of 10.[27,32] Lower socioeconomic classes have higher infection rates, although the ratio of chlamydial to gonococcal infection rates in these populations tends to be lower than in the more affluent classes.

Age is the most important factor for *C trachomatis* infection. Younger women have the highest infection rates. In approximately one in six sexually active teenagers attending adolescent clinics, *C trachomatis* was cultured from the cervix during routine pelvic examinations.[27] Other risk factors have been identified. Use of oral contraceptives is associated with higher chlamydial infection rates.[34] Race (which may be a proxy for socioeconomic status) is also a risk factor: black women have been found to have higher infection rates. Sexual preference is another risk factor: *C trachomatis* is a more common cause of urethritis in heterosexual males than in homosexual males.

C trachomatis genital tract infections are widely spread in our society. Persons with *C trachomatis* infection, usually urethritis in men, differ from those with gonococcal infection in socioeconomic characteristics. They typically have higher socioeconomic status (i.e., higher income or education), are more likely to be white, and are usually less sexually active and less likely to have had previous gonorrhea. This depiction of *C trachomatis* as an upper-class STD is misleading. *C trachomatis* is more common than gonorrhea among socioeconomically disadvantaged persons. In fact, *C trachomatis* infections are more likely to occur in young black men and women. However, the "upper-class STD classification" is based on the fact that gonorrhea is less likely to occur in higher socioeconomic groups. *C trachomatis* affects all socioeconomic groups.

Neonatal Infections. Approximately 60% of infants exposed to *C trachomatis* during birth contract the infection.[35] Approximately one in three exposed infants develops conjunctivitis, and one in six develops pneumonia. The incubation period for conjunctivitis is approximately one to three weeks, while most of the cases of pneumonia occur in the second and third month of life. In the United States an estimated 5% of pregnant women have cervical chlamydial infection, placing their infants at risk.

Lymphogranuloma Venereum. Lymphogranuloma venereum (LGV), a sexually transmitted disease, occurs in most parts of the world.[36] In some countries, especially in Africa and Asia, it is a major cause of morbidity, as reflected in patient visits to venereal disease clinics. In the United States LGV is relatively uncommon; only a few hundred cases are reported each year. This statistic is somewhat misleading because the diagnosis is almost always established by positive complement fixation (CF) tests on young men with inguinal lymphadenopathy. In fact, the anorectal syndrome is probably more common in the United States than the bubonic form of disease. That diagnosis is seldom established except from specialized laboratories.

Chlamydia psittaci

This infection is usually spread by the aerosol route with human infection almost always occurring as a result of exposure to infected avian species.[1] Most human infections are attributed to exposure to infected pet birds, usually exotic psittacine varieties or parakeets. Infection in these birds may be symptomatic, or it may be inapparent. The birds usually have gastrointestinal tract infections. It is likely that infection is spread by aerosol from infective droppings. The human disease is also recognized as an occupational hazard within the poultry industry, particularly to workers in turkey processing plants. In Europe ducks are a common source of human infections. Although human-to-human transmission has been described—particularly in some very severe outbreaks of pneumonitis due to *C psittaci*—such transmission is uncommon. Some fatal secondary cases have been developed in hospital personnel attending severely ill patients with primary cases. However, such outbreaks occurred prior to the introduction of tetracycline therapy.

Occasional human infections occur with *C psittaci* derived from mammals.

Chlamydia pneumoniae

C pneumoniae infections may be cyclical in the population. Studies from Scandinavia have identified periodic outbreaks.[37] In military trainees in Finland there were four separate outbreaks of pneumonia over a 10-year period. Approximately 6% to 8% of the recruits developed relatively mild pneumonias. National laboratories in Scandinavia have noted periodic excesses of ornithosis as confirmed by CF test. Retrospective evaluation of the sera from those cases, using type-specific microimmunofluorescence tests, showed that in nonepidemic years approximately 10% of the seroconversions were due to *C pneumoniae*.[38] In contrast, in the years showing large increases in presumed ornithosis, approximately 50% to 70% of the sera showed type-specific increases in antibody titer to *C pneumoniae*.

Either asymptomatic or very mild infections with *C pneumoniae* must be common as judged by seroprevalence studies.[22,23] Infections appear to begin relatively early in childhood, rarely in infancy. The age-specific seroprevalence rates reach 30% to 40% of the population at approximately 30 years of age. In most areas studied, 40% to 65% of the overall adult population have shown evidence of *C pneumoniae* infection.

Most of the *C pneumoniae* infections that have been detected have been in young adults in whom the disease appears to be relatively mild and clinically indistinguishable from mycoplasma pneumonia.[22,37] These clinically apparent cases occur at rates similar to those seen for infections with *Mycoplasma pneumoniae* or influenza A virus. In older individuals with underlying illnesses, *C pneumoniae* can cause fatal disease[39] and, similarly, young children in the developing world may have fatal pneumonias due to this organism.[40] In the older individuals with underlying disease, approximately half of the diagnosed cases appear to be hospital acquired rather than community acquired. There are two possible explanations for this: (1) perhaps *C pneumoniae* is being transmitted from other infected individuals in the hospital, or (2) perhaps these patients are

long-term carriers of *C pneumoniae* in whom, as a result of intubation, manipulation, and general debilitation, the infection activates to cause pneumonia. All other chlamydiae are known to cause chronic and clinically inapparent infections. Thus it would not be surprising to see inapparent *C pneumoniae* infections that become clinically active.

Pathogenesis and Pathology

Chlamydial diseases affect diverse anatomic sites in a number of hosts. Although it is impossible to describe universal pathologic changes, some common features in the host response to chlamydial infections are noteworthy.[41] Typically in the early inflammatory reactions, polymorphonuclear (PMN) leukocytic infiltrates, particularly at the superficial epithelium, accumulate at luminal or surface sites. If there is a particularly exuberant acute response, pseudomembranes may form, as the cellular reaction is enmeshed within the fibrin that is deposited. Such lesions may be seen on the conjunctiva of infants with inclusion conjunctivitis or over the liver in perihepatitis in birds and humans. The inflammatory response soon changes to a mixed and even predominantly mononuclear cell response. Macrophages are particularly common in LGV and *C psittaci* infections. Lymphocytes and plasma cells are commonly found in human *C trachomatis* infections. Because chronicity is characteristic of chlamydial infection, there are often long-term persistent changes with low-grade inflammatory reactions.

Chlamydia trachomatis

The molecular basis of chlamydial pathogenicity is unclear. Studies in cell culture systems have identified a number of virulence factors that appear to be important in establishing infection.[42,43] These include the ability to recognize specific attachment sites, the ability to induce phagocytosis, and the ability to avoid phagolysosomal fusion.

Members of the trachoma biovar of *C trachomatis* are parasites of columnar epithelial cells and appear to cause disease in most anatomic sites where these cells are found. These organisms are primarily pathogens of the conjunctivae and genital tract, in which these cells predominate. The organisms can also be important pathogens in the lower gastrointestinal tract and respiratory tract. The LGV biovar has a broader host cell range, involving lymphoid and endothelial cells. It is more invasive and apparently capable of causing more tissue destruction as a result of the infectious process; late stages of LGV are often characterized by scar formation.

The trachoma biovar seems incapable of infecting enough cells to cause the tissue damage that appears in some of its diseases. Immunologic mechanisms for pathogenesis have been postulated.[14] More severe disease is often seen in secondary infection and in reinfection with heterologous biovars. A soluble extract from chlamydial particles can induce marked conjunctival inflammation in animals sensitized by a prior infection.[44] Thus, it seems that much of the pathogenesis of the trachoma biovar disease results from local hypersensitivity reactions.

The antigen responsible for the hypersensitivity reactions has been identified as a 57 Kd protein with genus-specific antigenic reactivity.[45] This leads to the speculation that prior chlamydial infection with any species could sensitize to a first infection with another species and therefore exacerbate its outcome.

With *C trachomatis,* that severe outcome is ultimately characterized by fibrosis. In trachoma the blinding lesion is scarring of the conjunctiva. Over time, contraction of these scars results in the lid distortion that causes corneal damage. In acute salpingitis the fallopian tube is scarred, leading to ectopic pregnancy or tubal factor infertility. In late LGV the genital and lower gastrointestinal tracts are extensively scarred.[36,46]

One common result of the trachoma biovar infection is the induction of lymphoid follicles.[1,41] Follicle formation in the conjunctiva is a hallmark of trachoma and inclusion conjunctivitis. Similar lesions have been observed in genital tract sites infected with the trachoma biovar.[47] These are true lymphoid follicles with germinal centers and a B cell predominance, although T cells are often found infiltrating the subepithelial spaces between the follicles.

LGV infection can result in giant cell and granuloma formation.[36,46] LGV lesions are also characterized by necrosis with formation of stellate abscesses. When an infection is restricted to the lymph nodes there is marked hyperplasia and transformation of macrophages into epithelioid cells. The entire process results in considerable necrosis, and large fluctuant bubos may develop.

The mechanisms involved in inducing conjunctival scarring are not clear, but it is thought to result from necrosis of follicles. It is interesting to consider that end-stage disease for LGV and trachoma biovars, in different anatomic sites, is a result of scar formation. Thus, the rectal strictures of LGV can be viewed in a sense to be analogous to the conjunctival scarring that ultimately results in blindness in trachoma and to the fallopian tube scarring that results in infertility after acute salpingitis.

Chlamydia psittaci

C psittaci is capable of infecting a wide variety of cells and of damaging most anatomic sites, probably due to the cytocidal effect of the infection. The typical sequence of acute and chronic inflammation occurs with *C psittaci* infections as well. Often the lung infections are complicated by secondary bacterial infections that obscure the characteristic pathologic picture. Inclusions of *C psittaci* can be demonstrated in alveolar macrophages and epithelial cells. The organisms can spread via the blood stream to involve many other sites.

Clinical Manifestations

Chlamydia trachomatis

Trachoma. Trachoma is a chronic keratoconjunctivitis caused by *C trachomatis.*[1,14,25] It may begin as a mucopurulent conjunctivitis and is often complicated by secondary bacterial infection. Marked follicular reaction and papillary hypertrophy develop. In hyperendemic areas most active disease is seen in young children. As the follicular reaction resolves, some focal necrosis may occur and scarring of the upper conjunctivae can develop. Over time, these scars contract and cause an inturning of the upper eyelids, so that the eyelashes abrade the cornea (Figure 3). These lesions (trichiasis and entropion) cause the blindness in trachoma. It takes many years for sufficient contraction of scars to occur to cause the lid distortion. Blindness therefore generally occurs more than 25 to 30 years after the peak of the active inflammatory processes. Mild cases of trachoma rarely lead to visual loss.

Inclusion Conjunctivitis. Inclusion conjunctivitis in adults or in newborn infants, also called paratrachoma, is usually relatively mild and self-limited. It results from inoculation of conjunctivae with genital tract discharges. Adults probably acquire the infection during sexual activity or by hand-to-eye transmission, while newborns acquire

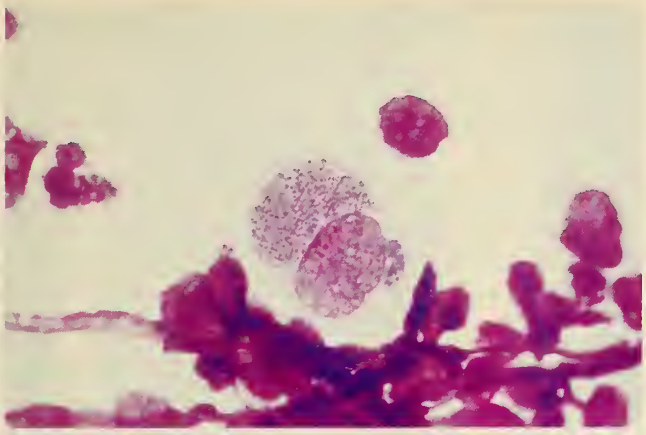

Figure 1.—Chlamydial intracytoplasmic inclusion in epithelial cell Giemsa-stained conjunctival scraping from a patient with trachoma.

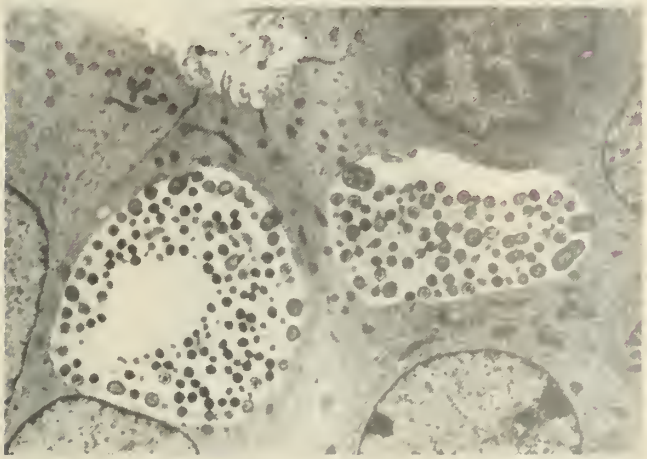

Figure 2.—Electron micrograph of *C trachomatis* inclusions in epithelial cells of mouse oviduct.[100] Note that inclusion contains both small elementary bodies and larger reticulate bodies. (Courtesy of D. Philips.)

the organism during birth.[35] The incubation period is typically between 6 and 19 days.[1] In adults the disease is follicular; infants, having a less developed lymphoid response, usually have mucopurulent conjunctivitis. Although micropannus and minor scarring may develop, severe disease with a poor prognosis occurs uncommonly.

Genital Tract Infections

Nongonococcal Urethritis. Nongonococcal urethritis (NGU) is probably the most common manifestation of *C trachomatis* infection of the genital tract[48] (Table 2). Approximately one third to one half of men with NGU have a demonstrable *C trachomatis* infection of the urethra.[49] Postgonococcal urethritis, a specific subset of NGU, occurs in men who have been successfully treated for gonorrhea.[50] Most had concomitant chlamydial infection. Gonorrhea is the major risk factor for *C trachomatis* infection of the genital tract. Approximately 20% of men and 40% of women who have *Neisseria gonorrhoeae* in their genital tracts will also have a concurrent *C trachomatis* infection.[51] Thus, the Centers for Disease Control recommend that heterosexual males and females with gonorrhea be given a course of antichlamydial therapy immediately after the β-lactam prescribed for treatment of the gonococcal infection. If this is not done, most of the men will develop postgonococcal urethritis. The women will develop postgonococcal cervicitis, but most importantly many will subsequently develop acute salpingitis.[52] An additional week of tetracycline therapy can prevent this.

TABLE 2.—*Contribution of* Chlamydia trachomatis *to Selected Clinical Syndromes*

Men	Nongonococcal urethritis	30-50%
	Postgonococcal urethritis	70-90%
	Epididymitis (<35 years)	60%
Women	Mucopurulent endocervicitis	40-60%
	Acute salpingitis	25-50%
Infants	Conjunctivitis (<1 month)	25-50%
	Pneumonia (<6 months)	30-50%

Figure 3.—Late stage of trachoma showing eyelashes abrading the cornea.

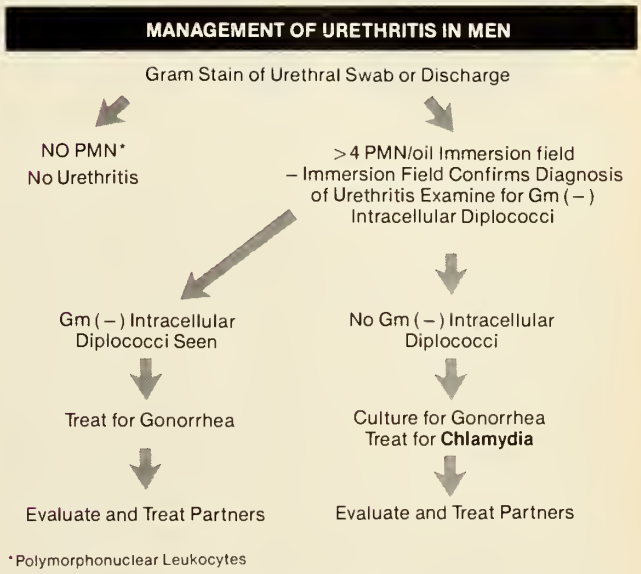

Figure 4.—Management principles of urethral infections of males.

Nongonococcal urethritis cannot be distinguished from gonococcal urethritis on clinical grounds. Men with gonorrhea are more likely to have a yellowish purulent discharge; men with nongonococcal urethritis tend to have a scant mucoid discharge that often can be elicited only by stripping the urethra. However, these statistical distinctions are not reliable in individual cases. It is beneficial to have a specific etiologic diagnosis for purposes of contact tracing and treatment, but urethritis in the male can be managed successfully without doing tests for *C trachomatis* (Figure 4). The approach is based on diagnosis by exclusion. To define the urethritis, a Gram stain smear of an endourethral swab or a discharge is made to see if polymorphonuclear

Figure 5.—Severe mucopurulent endocervicitis showing inflamed cervix with purulent discharge from the os. (Courtesy of E. B. Rees.)

leukocytes are present. If intracellular diplococci are found, a man should be treated for gonorrhea, followed by treatment for *C trachomatis*. If intracellular diplococci are not seen, culture tests for gonorrhea should be done at the same time that immediate treatment for nongonococcal urethritis is being given. In either instance partners should be examined and treated.

Approximately 1% to 2% of men with urethritis will develop epididymitis. *C trachomatis* and *N gonorrhoeae* are the usual causes of this condition in young, sexually active men.[53] Reflecting the relative prevalence of these pathogens, chlamydial epididymitis is about twice as frequent as gonococcal epididymitis.

A similarly small proportion of men with NGU will later develop Reiter's syndrome, or sexually acquired reactive arthritis (SARA). Many of the men with SARA have had chlamydial infection and increased immune responses to chlamydial antigens. Chlamydial antigens or particles have been found in joints of some of these men, but the true relationship of chlamydial infection to the disease is not yet clear.[54]

Cervicitis. C trachomatis causes a mucopurulent endocervicitis in women[55] (Figure 5), identified by: (1) the presence of a mucopurulent discharge from the endocervical os (by microscopy there should be more than 10 polymorphonuclear leukocytes per oil immersion field in a Gram stain smear of endocervical material), and (2) induced bleeding when a swab is rubbed against the wall of the endocervical canal. Swab tests can be used to demonstrate a purulent discharge (a white swab inserted in the endocervical canal will be colored yellow in the presence of a purulent discharge) or easily induced bleeding (a swab rubbed against the endocervical wall will be reddened by bleeding caused by pressure if the cervix is edematous and inflamed) (Figure 6). This condition is relatively common in patients attending STD clinics, and these diagnostic criteria have a predictive value for chlamydial infection of approximately 30% to 50% in that setting. Gonorrhea is the only other bacterial infection likely to be associated with mucopurulent endocervicitis. It has been suggested that presumptive treatment for a chlamydial infection should automatically be

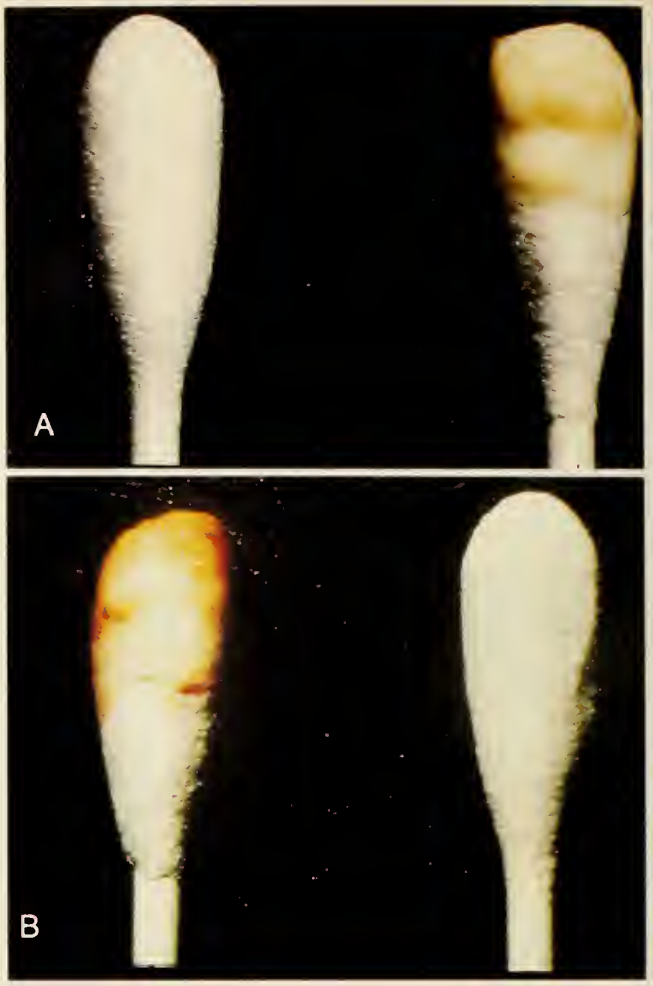

Figure 6.—Swab tests for mucopurulent endocervicitis. The swab is **(A)** colored yellow if there is pus in the endocervical canal; and **(B)** blood tinged after being rotated against the wall of the endocervical canal if it is inflamed. (Courtesy of J. Paavonen.)

given when this syndrome is noted, with the expectation that the tetracycline regimens used for *Chlamydia* would be effective for most gonococcal infections.

Women with gonorrhea who have a mucopurulent cervical discharge tend to maintain that discharge if they also have a chlamydial infection and are treated with beta-lactam drugs alone. Thus, the same rationale and regimens for treatment of women with gonorrhea as were discussed above have been applied for men with gonococcal infection. The same regimens are used. It is even more important to treat women with gonorrhea for concurrent chlamydial infection on a presumptive basis. Women appear to have infection rates approximately twice as high as are observed with men. (35% to 45% of women with gonorrhea have concomitant chlamydial infection.) Eradication of the chlamydiae will reduce the subsequent development of salpingitis.[49]

Chlamydial cervicitis is serious in that it is a precursor for ascending infection. Many women who have *C trachomatis* in the cervix also have endometrial infection.[56] The rate at which infections ascend is not known, but in one study results in 25% of those women at risk for such an infection were positive. *C trachomatis* can cause either clinically overt salpingitis or an inapparent salpingitis. Fallopian tube damage, causing tubal factor infertility or ectopic pregnancies, can occur from inapparent infection as well as from a clinical episode of pelvic inflammatory disease.

Pelvic Inflammatory Disease. Women are most severely affected by infections with *C trachomatis* (Table 3). Pelvic inflammatory disease, the most important consequence of genital chlamydial infection,[57] has a broad clinical spectrum. The term pelvic inflammatory disease (PID) is preferable to the term acute salpingitis because the infection is not restricted to the fallopian tubes. Most women with salpingitis caused by either *C trachomatis* or *N gonorrhoeae* also have endometritis.[58] Inapparent salpingitis appears to be relatively common. The only truly reliable way of diagnosing acute salpingitis is by laparoscopy. Routine use of this procedure has helped to clarify the natural history of chlamydial salpingitis. Chlamydial salpingitis can have a milder clinical presentation than salpingitis caused by other microbes.[57] Indeed this has led to the introduction of more relaxed criteria for the clinical diagnosis for acute salpingitis (Table 4). Women with chlamydial salpingitis differ from women with gonococcal or nongonococcal, nonchlamydial salpingitis in typically being younger, having a longer duration of symptoms prior to seeking medical attention, and being less likely to be febrile. Paradoxically, the chlamydia-positive cases are more likely to involve an elevated sedimentation rate and severe inflammatory changes of the fallopian tube by laparoscopy. Thus, the picture which emerges suggests that while the clinical presentation may be mild, the tubal involvement may be severe. This conclusion is supported by the seroepidemiologic studies that show *C trachomatis* to be a major risk factor in tubal factor infertility and ectopic pregnancies and that most of the women with these complications do not have a prior history of a clinical episode of PID.[59]

Ascending genital infection is common. *C trachomatis* is found in the endometrium or fallopian tubes of approximately 25% to 50% of women with acute salpingitis in the United States and at higher rates in western Europe. *C trachomatis* is also associated with complications of salpingitis, such as the Fitz-Hugh–Curtis syndrome (perihepatitis).[60] Unfortunately, because chlamydial salpingitis can be clinically mild, or even inapparent, evidence of chlamydial infection is often first obtained retrospectively by serologic tests performed during evaluation of infertility.

TABLE 3.—*Impact of* Chlamydia trachomatis *in the United States*

	Annual Infection: 4,000,000	
Men	1,000,000	Nongonococcal urethritis
	200,000	Epididymitis
Women	>250,000	Pelvic inflammatory disease
	50,000	Rendered infertile
	35,000	Ectopic pregnancies
Infants	60,000	Conjunctivitis
	35,000	Pneumonia
	20,000	Chronic lung damage

TABLE 4.—*Diagnostic Criteria for Acute Salpingitis*

All present:
1. Lower abdominal pain and tenderness
2. Cervical motion tenderness
3. Adnexal tenderness

Minimum of one present:
1. Temp >100.4°F (38°C)
2. WBC >10,000
3. ESR elevated
4. Inflammatory adnexal mass
5. Purulent fluid obtained via culdocentesis

Other Genital Tract Conditions. Approximately 6% of asymptomatic gay men attending venereal disease clinics were found to have *Chlamydia* by rectal swabs, as compared to a 12% recovery rate from men with proctitis.[61] *C trachomatis* can be recovered from the pharynx of sexually active males or females at risk for genital tract infection.[62] The role of this agent in causing pharyngitis is uncertain. Most of the evidence associating *C trachomatis* with pharyngitis was based on serologic tests. It is now thought that these were measuring cross-reacting antibodies to *C pneumoniae.*[63]

C trachomatis may also cause bartholinitis.[64] Urethral infections also occur in women, and chlamydial infection has been associated with sterile pyuria in some female populations.[65] This association of chlamydial infection with the urethral syndrome was shown in college-age women. It is probably unwise to generalize those findings to other populations of women.

The role of chlamydiae in complications of pregnancy is controversial. In some studies *C trachomatis* infection has been associated with stillbirths, prematurity, or small for gestational-age infants.[66-68] Other studies have found no effects, or very modest ones, of chlamydial infection on pregnancy outcome.[69,70] It is not clear whether these discrepant results reflect population differences or the confounding effects of other genital infections.

C trachomatis can cause postpartum complications. The organism has been associated with postpartum endometritis and salpingitis.[71] Women with chlamydial infection are at risk of similar outcomes after induced abortions. Testing women for chlamydial infection, and treatment with a tetracycline, of those infected, has been shown to reduce postabortal complications.[72]

Neonatal Infections

Approximately 5 to 21 days after birth, the infant with a chlamydial infection develops mucopurulent conjunctivitis.[35] Hyperemia and discharge are the most prominent findings. Follicles are not seen unless the condition persists for longer than a month. Inclusion conjunctivitis of the newborn (ICN) is usually self-limiting and will resolve in a few months without treatment. ICN is not considered to be a sight-threatening condition. Corneal damage is minimal, although some keratitis and micropannus can develop. Conjunctival scarring is relatively uncommon, although sheet scarring may follow the disease in infants who develop pseudomembranes.[1] These scars do not result in lid deformity. Occasional cases persist and severe disease that may threaten vision can rarely develop.

The incubation period for chlamydial pneumonia of infants is usually between 2 and 12 weeks.[19,35] The infants often have a prodrome of rhinitis and many have had conjunctivitis. Affected infants are usually afebrile, are markedly tachypneic and occasionally apneic, and have a staccato cough. They are hypergammaglobulinemic, particularly in the IgM class. A relative eosinophilia occurs in approximately one third of affected infants. Radiographs usually show hyperinflation.

The spectrum of chlamydial respiratory involvement in infants is quite broad. Nasopharyngeal infections are common.[19,35] Some infants develop severe rhinitis, without lower respiratory involvement, that can occasionally interfere with respiration.[73] The pathogenesis of chlamydia pneumonia probably reflects descending infection, and bronchiolitis can also occur.[74] Infants with chlamydia pneu-

monia typically fall into the category of "failure to thrive" and often have only mild respiratory distress, with tachypnea being the prominent finding. Occasionally these infants have severe respiratory problems and may become apneic and require respiratory assistance. Approximately three-quarters of the infants with pneumonia can be managed on an outpatient basis. The other infants are severely ill and must be treated in an intensive care nursery. This can be a life-threatening condition.

Serous otitis media is reported as a complication of the pneumonia and may occur independently. Infants with chlamydia pneumonia may subsequently develop chronic respiratory problems.[75] Severe rhinitis has also been associated with chlamydial infection in the newborn.[73] Gastrointestinal tract infections occur but no corresponding clinical manifestations have been described.[76]

Lymphogranuloma Venereum

This venereal disease is caused by three serovars within the species *C trachomatis.*[14] These organisms are also biovars, as they are more invasive and the disease is a systemic one. The LGV organism may be recovered from genital ulcers and may also be present in the cervix or urethra in an asymptomatic form. It is transmitted by sexual activity.

The incubation period is variable (usually one to three weeks, but it may be much longer). The first manifestation of the disease appears to be a primary lesion—a painless superficial ulcer or vesicle on the genitals. In temperate climes this lesion is often not apparent.[77] In tropical countries, the ulcerative form of the disease appears to be quite important. Within one to three weeks after the primary lesion appears, regional lymphadenopathy develops. Bubo development is known as the secondary stage of the disease and is typically seen in young men. Women probably have primary implantation of the organism within the vagina, where the draining lymph nodes are retroperitoneal rather than inguinal. Thus these women usually do not develop inguinal lymphadenopathy. The lymph nodes ultimately heal, often with some scarring, but the infection can persist and cause late destructive lesions involving the gastrointestinal tract and genitalia. Scarring can result in obstruction, and fistulas are common. Primary implantation within the rectum can result in a severe proctocolitis. This is not an uncommon condition among homosexual men in some parts of the United States.[36,78]

The anorectal syndrome can manifest itself in a number of different ways. There can be acute hemorrhagic proctitis or proctocolitis. Usually a bloody mucopurulent discharge is seen. The rectum and sometimes the colon are inflamed and often ulcerated. In another form of the condition the lesions are more proximal in the intestinal tract and rectal involvement is not obvious. For the diagnosis of proctocolitis, specimens are collected from the colon by a proctoscopic or endoscopic examination. Biopsies show giant cells and granuloma formation. The organism is found in subepithelial tissues. Men with this condition are often systemically ill with fever, chills, and weight loss. In 270 men examined for this condition in San Francisco and in whom typical causes of proctitis such as *Herpesvirus hominis,* syphilis, or gonorrhea had been ruled out, *C trachomatis* was isolated from biopsies of 24%, and 70% of the isolates that were typed were LGV strains. These patients tended to be quite ill and had been referred to gastrointestinal or infectious disease clinics for further evaluation. It is likely that this condition is not uncommon but that the diagnosis is often missed.

Although the primary sites involved usually are within the genitourinary tract, if the organism is implanted elsewhere, local disease may occur. For example, if the eye is the site of infection, a form of Parinaud's oculoglandular syndrome may develop. Implantation within the oral cavity may result in cervical lymphadenopathy. Systemic complications, including hepatitis, pneumonia, arthritis, and meningoencephalitis, have been described.

Chlamydia psittaci

Psittacosis is the name used for the human infection with *C psittaci.* In most cases, exposure to birds can be documented. The route of infection is via the respiratory tract. The incubation period is usually between 7 and 14 days, although a much wider range is recognized. The prodrome is relatively nonspecific. Infections are often subclinical and may be mild, resembling a common cold or a mild influenza attack, but severe pneumonitis may occur. In symptomatic cases fever, chills, and severe headache usually occur. Atypical pneumonia is a common presentation. Radiographs may show more extensive lung involvement than is expected on the basis of respiratory difficulty. The pulse rate may be lower than expected from the degree of fever and the general toxicity.

Alternatively, the disease may present with a general toxic, febrile state without respiratory findings. Overt clinical disease is almost always accompanied by fever and severe headache. Cough, when present, is usually nonproductive, but radiographs show extensive pneumonic involvement. Hepatosplenomegaly is common. Person-to-person transmission is uncommon. Prior to antibiotic therapy the case fatality rate was quite high ($>20\%$), with most fatalities seen in those above the age of 50 years. Treatment of psittacosis with tetracycline is almost always successful and fatalities are rare, although the clinical response may not be rapid and recovery may be prolonged. Many complications are recognized, including meningoencephalitis, myocarditis, and hepatitis.

C psittaci can involve multiple organs. Although it has long been recognized that the agent can be associated with myocarditis in severe cases, there have recently been a number of reports of valvular involvement. In most cases the aortic valve has been involved and replacement has been required. The diagnosis in many of these cases has not been totally convincing. Pneumonia was not commonly found and *C psittaci* has not been isolated from specific lesions or the blood.

A number of pregnant women exposed to *Chlamydia*-infected sheep have had spontaneous abortions.[21] The organisms have been recovered from placental tissues and from other organs in fatal cases. Although the incidence of this infection is not known, *Chlamydia*-infected sheep clearly represent a threat to the health of pregnant women.

Chlamydia pneumoniae

C pneumoniae infections cause a variety of respiratory diseases,[24] typically a mild atypical pneumonia in young adults. The disease is clinically indistinguishable from pneumonias due to *Mycoplasma pneumoniae* or influenza viruses, even in older debilitated individuals in whom fatal outcomes have been observed. The diagnoses have depended upon specific microbiologic evaluations.

Diagnosis

The diagnosis of chlamydial infections is similar to diagnosis of other bacterial infections.[79] The organism can be

demonstrated in smears from infected sites; the agent can be isolated; and antibodies can be measured. Unfortunately, because chlamydiae are obligate intracellular parasites, they cannot be cultured on artificial media; cell culture systems must be used for isolation. These procedures require specialized laboratories and thus restrict clinicians' access to chlamydial diagnosis. Recently the revolution in biotechnology has resulted in the introduction of a number of nonculture tests for diagnosis of *C trachomatis* infection. Although these tests are not as sensitive as culture done under ideal circumstances, they are far more widely available and have greatly improved access to laboratory diagnosis of chlamydial infection. One major problem in the diagnosis of these infections is adequate specimen collection. A common mistake is to collect discharges from affected sites for laboratory tests. This is inappropriate. Chlamydiae are intracellular parasites. It is therefore imperative for most tests that an adequate specimen of the affected mucous membranes should be cleaned of discharge, after which specimens are collected by rubbing swabs briskly on the epithelial cell surfaces. For specimens from the female genital tract the use of cytobrushes is to be preferred over swabs.[80]

Although culture is clearly the most sensitive test, it requires maintenance of a cold chain to protect viability of the organism. The nonculture tests are better suited when transportation problems exist, or when a cold chain cannot be maintained, because they do not require viability for a positive result. The two most commonly used tests are a direct fluorescent antibody (DFA) test and an enzyme immunoassay (EIA) procedure.[81,82] They have comparable performance profiles, with sensitivity of 75% to 85% and specificity of 97% to 98%. The DFAs that provide the best morphologic identification use monoclonal antibodies against a species-specific epitope on the MOMP molecule.[83] They will stain only elementary bodies of *C trachomatis*. The EIAs are usually directed at the genus-specific lipopolysaccharide and thus should react with all chlamydial species. The DFA allows assessment of specimen adequacy. The EIA is more suitable for processing large numbers of specimens.

In general the test of choice for isolation of chlamydia involves inoculation by centrifugation of McCoy cells that are then treated with cycloheximide.[84] This antimetabolite favors the growth of chlamydiae in mammalian cells. Presence of the organism is demonstrated by specific staining for inclusions. It will take at least 48 to 72 hours for the laboratory to return a positive result. EIA and DFA results can be reported in less than 24 hours.

Chlamydia trachomatis

Trachoma. The diagnosis of trachoma is essentially made on clinical criteria.[85] Chlamydiae are difficult to detect in mild cases. In severe active cases, typically only 30% to 60% of conjunctival specimens will test positive for chlamydiae. The classical test, demonstration of inclusion by Giemsa stain, is now recognized to be insensitive.[86]

Genital Infection. Definitive diagnosis of genital infections is made by isolation of the agent in cell culture systems. Nonculture methods for chlamydial diagnosis are widely used. However, these tests, while being simpler and perhaps less expensive than cell culture systems, appear to be less sensitive. All of the nonculture tests have some false-positive results. Thus, they may not be suitable for use in low prevalence settings when the predictive value of a positive test will be low.[87] Nonculture tests should never be used when a result is being sought for legal purposes, such as in cases of rape or child abuse.

It should be stressed that some of the chlamydial diseases can be managed without a specific diagnosis. For example, urethritis in men can be managed easily on the basis of Gram stain (see Figure 4). In other instances, presumptive treatment is given based on clinical findings (Table 5). For example, women with mucopurulent endocervicitis or salpingitis should be automatically treated for chlamydial infection. Evaluation and treatment of sex partners is indicated in all of these conditions.

Serology is not useful in diagnosing uncomplicated genital tract infections, although the higher antibody titers seen by the microimmunofluorescence (micro-IF) test in complications (e.g., epididymitis, salpingitis, Fitz-Hugh–Curtis syndrome) may provide some support for an etiologic diagnosis.[88] Seroconversion may occur in a first infection with *C trachomatis*, but its detection will take several weeks and is therefore seldom clinically relevant.[89]

Neonatal Infections. Conjunctivitis can be diagnosed readily by any of the cytologic tests. Giemsa stain is adequate in diagnosing severe cases of conjunctivitis, while the DFA and EIA techniques are quite sensitive.[90] The agent can be easily isolated.

Although a specific diagnosis for pneumonia may be more difficult because of sampling problems, the organism can often be isolated from the nasopharynx or tracheobronchial aspirates.[19,35] Serology may be the test of choice in diagnosing chlamydial pneumonia because of the sampling problems.[91] Infants with chlamydial pneumonia almost always develop high IgM antibody levels. Because of their defined exposure (at birth), the diagnosis can be readily established on the basis of a single point titer of specific

TABLE 5.—*Treatment of Chlamydial Infections*

	First Choice		Second Choice	
Organism and Condition	*Drug*	*Dose*	*Drug*	*Dose*
C psittaci				
Psittacosis	Doxycycline*	100 mg b.i.d. × 3 wk	Erythromycin	250 mg q.i.d. × 3 wk
C pneumoniae				
Respiratory	Doxycycline	100 mg b.i.d. × 3 wk	Erythromycin	250 mg q.i.d. × 3 wk
C trachomatis				
LGV	Doxycycline	100 mg b.i.d. × 3 wk	Sulfamethoxazole	1 g b.i.d. × 3 wk
Trachoma biovar				
Genital tract infections (e.g., urethritis, cervicitis)	Doxycycline	100 mg b.i.d. × 1 wk	Erythromycin	500 mg q.i.d. × 1 wk
In pregnant women	Erythromycin	500 mg q.i.d. × 1 wk	Amoxicillin	500 mg t.i.d. × 1 wk
Infant pneumonia or inclusion conjunctivitis (infants)	Erythromycin	10 mg/kg q.i.d. × 2 wk	Sulfisoxazole	37.5 mg/g q.i.d. × 2 wk
Inclusion conjunctivitis (adults)	Doxycycline	100 mg/kg b.i.d. × 2 wk	Sulfisoxazole	37.5 mg/g q.i.d. × 2 wk

*Tetracycline 500 mg q.i.d. is considered to be the therapeutic equivalent of doxycycline 100 mg b.i.d. As doxycycline has become less expensive, it has become preferred because of potential advantages in compliance.

antichlamydial IgM antibodies, more than 1:32 in the micro-IF test.

Lymphogranuloma Venereum. LGV results in relatively high complement-fixing (CF) antibody levels and the CF test can be used to support a diagnosis. The micro-IF test can be used the same way, and very high titers of broadly reactive antibody are usually found.[92] Chlamydiae can be isolated from ulcers, lymph node aspirates, rectal swabs, or biopsies. DFA can also be used. In the past, the diagnosis was based on the use of a delayed hypersensitivity skin test (Frei test). This test is not recommended because of problems with sensitivity and specificity.[76] It is not available in the United States but is still available in some other countries.

Chlamydia psittaci

Clinical signs are not pathognomonic, although a relatively low pulse associated with a high fever and severe headache can be suggestive in a patient with pneumonitis. The physician's index of suspicion (asking questions about potential exposure to birds) is usually crucial to arriving at a diagnosis. Serodiagnosis is generally considered to be the method of choice because isolation of the agent is seldom achieved. Rising antibody levels can be demonstrated by CF or micro-IF tests.

Chlamydia pneumoniae

The diagnosis of *C pneumoniae* infection is relatively difficult. The organism does not grow well in cell culture systems. It can be isolated from throat swabs, and HeLa cells appear to be the most susceptible cell line. More often the diagnosis is established on serologic grounds. Approximately 50% of cases will show fourfold or greater rises in CF titers. Seroconversion, high ($\geq$ 1:512) IgG antibody levels, or IgM ($\geq$ 1:32) levels in the specific microimmunofluorescence tests are the usual diagnostic criteria.[24] Seroconversion may take four weeks.

Treatment

Chlamydia trachomatis

Trachoma. To prevent blindness in the hyperendemic areas, WHO recommends intermittent topical therapy with 1% tetracycline ointment.[93] In the typical setting this is given to all school children or young children in a village once or twice daily for six consecutive days on a twice yearly schedule. This regimen will not cure trachoma, but it will reduce the severity of the disease and thus prevent blindness. Oral therapy is appropriate for individual cases but cannot be easily administered on a mass basis in endemic areas.

TABLE 6.—*Syndromes Calling for Presumptive Treatment for* C trachomatis

Syndrome	*Expected Chlamydial Infection Rates*
A. Men	
Nongonococcal urethritis	25-50%
Gonorrhea	20%
Epididymitis (in young men)	60%
B. Women	
Mucopurulent endocervicitis	30-50%
Pelvic inflammatory disease	25-50%
Gonorrhea	35-45%
Partner with NGU	30%
Partner with *Chlamydia*	65%

Genital Infections. Treatment of uncomplicated genital tract infection is relatively easy with 2 g tetracycline/day for 7 days. This program results in cure rates in excess of 95%.[29] Upper genital tract infections require longer courses of therapy. Short-term therapy plays no role in management of chlamydial infections (Table 6).

Infant Infections. Chlamydial infection in the infant calls for systemic therapy with erythromycin (50 mg/kg in divided doses each day). Conjunctivitis will respond to 7 to 10 days of therapy, while pneumonia should be treated for 14 to 21 days. Topical therapy is not recommended for ICN because of relatively high failure rates and the fact that oral therapy will prevent subsequent development of pneumonia.

Lymphogranuloma Venereum. There are little data available from controlled treatment trials of lymphogranuloma venereum. Tetracyclines and sulfonamides have been used. The treatment of choice appears to be at least two weeks of tetracycline at 2 g/day. The response may be variable. In some instances, several courses of therapy appear to be necessary.

Chlamydia psittaci

Tetracycline, 2 g/day for at least two weeks, is considered the treatment of choice, with erythromycin being the alternative drug. Relapses are common if the patients are inadequately treated.

Chlamydia pneumoniae

These infections are treated as atypical pneumonias. The drugs of choice are tetracycline and erythromycin. No data are available from controlled treatment trials.

Prevention

There are no effective vaccines for human chlamydial infection.[1,14] The natural history of some of these infections, and the results of some experimental trachoma vaccine trials, suggest that a short-lived immunity can develop. Unfortunately, some vaccinees developed severe disease, and repeated infections are more likely to produce deleterious results. The importance of this evidence for immunopathology in chlamydial disease has been borne out with identification of a 57 Kd protein-sensitizing antigen.[45] Thus, there is now hope that modern techniques of molecular genetics will allow production of subunit vaccines free from sensitizing antigens.

Chlamydia trachomatis

Trachoma. Trachoma is a disease of poverty in developing countries. There are no control measures better than improvement in standard of living. Application of topical antibiotics will reduce severity of the disease and thus minimize the incidence of subsequent blindness. Corrective lid surgery is available to prevent development of blindness in those who already have lid deformity.

Sexually Transmitted Infections. Chlamydia control programs are only now being developed.[29] The Centers for Disease Control has recommended treatment guidelines for the management of chlamydial infections.[51] With the broader availability of diagnostic tests, the recommendation has been made that chlamydial infections be made reportable. Reporting of nongonococcal urethritis and PID (the former being the best proxy for chlamydial infections and the latter being the most important complication) should provide a firmer data base. In this way the prevalence and incidence of these conditions can be established. When high-risk pop-

ulations are better defined, control efforts can be implemented. It is likely that screening programs for asymptomatic sexually active individuals will yield higher rates of infection and be more cost effective for *C trachomatis* infection than they are for gonococcal infection. Routine treatment of all gonococcal infections with regimens effective against *C trachomatis* in heterosexuals will have some impact on the reservoir. About 500,000 of the 1.8 million annual cases of gonorrhea also involve chlamydial infections. The appropriate use of antichlamydial therapy on presumptive grounds in syndromes such as nongonococcal urethritis and mucopurulent endocervicitis will also have an effect. Contact tracing should be particularly productive in identifying new cases of *C trachomatis* infection because the reservoir is so large. The current efforts to promote condom use because of AIDS could benefit chlamydia control. Use of barrier contraceptives will reduce transmission.

In order to be effective, chlamydia control programs will have to attack the reservoir of infection. The interventions just described will help to reduce the reservoir but will leave many infected individuals untested. Even if routine screening for chlamydial infection is introduced for sexually active females at times when they have routine pelvic examinations, it will not address the issue of male carriers. Approximately 10% of asymptomatic, sexually active young men have urethral chlamydial infection.[94] It will require development of noninvasive tests that are acceptable to the asymptomatic males (urethral swabbing will not be) before screening programs can have a major impact.

Perinatal Infections. Infections in infants are preventable. A program of screening pregnant women and erythromycin treatment for those found to be infected will prevent perinatal chlamydial infection.[95] Use of topical erythromycin or tetracycline for ocular prophylaxis in the newborn may reduce inclusion conjunctivitis of the newborn but does not prevent it.[96] This regimen will not prevent pneumonia.

Chlamydia psittaci

Traditionally, the administrative method of controlling psittacosis derived from exotic birds has been by embargo. Importation of psittacine birds has been prohibited by many countries. Screening to select psittacosis-free birds for breeding has been used to establish uninfected flocks of those small birds that can be bred in captivity. Chemoprophylaxis for exotic birds has been developed.[97] If birds are held in quarantine and appropriately treated with tetracycline-containing feed, they can be cleared of *C psittaci* infection before they are introduced into normal distribution channels. When treated birds are introduced into commerce, clean premises can be maintained by keeping habitats closed and avoiding introduction of any untreated birds. Unfortunately, this approach will not work in the poultry industry because of potential contamination of premises by infected feral birds.[98]

Conclusions

As noted, chlamydiae are extremely common human pathogens, causing a broad spectrum of diseases. Human psittacosis, although long recognized, is probably the least important human chlamydial disease. It is not currently a major research area. *C pneumoniae* infections, on the other hand, have been described only in the last few years. This is the "hot" area in clinical research on chlamydial infections. It is obvious that this organism is widely distributed and that infection is common. This is a story that is unfolding.

In contrast, the torrent of new information on *C trachomatis* infections has slowed. After two decades of expansion of its clinical spectrum and increased awareness of the high prevalence of these infections, this is an area in consolidation. The application of techniques of molecular biology has rekindled hopes for a trachoma vaccine. There is need for such a vaccine. Trachoma remains the world's leading cause of preventable blindness. It has become obvious that the standard of living in many developing countries in which trachoma is endemic is not improving. With population growth, more people will be at risk of trachomatous blindness.

Sexually transmitted chlamydial infections remain a major public health problem. There is a clear need for an effective chlamydia control program.[99] The targets for reduction are well identified (see Table 3). These infections, and their consequences, cost billions of dollars each year. Thus control programs are almost certain to be cost effective. Given that reasonably accurate diagnostic tests are readily available and that these infections are easily treated, the lack of a control program is unacceptable.

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Tardive Dyskinesia

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Tardive dyskinesia is a potentially irreversible syndrome of involuntary hyperkinetic movements that occur in predisposed persons receiving extended neuroleptic (antipsychotic) drug therapy. It is usually characterized by choreoathetoid dyskinesias in the orofacial, limb, and truncal regions, but subtypes of this syndrome may include tardive dystonia and tardive akathisia. Although the mechanisms underlying the pathogenesis and pathophysiology of this disorder are unproven, altered dopaminergic functions will likely play a role in any explanation of it. Tardive dyskinesia develops in 20% of neuroleptic-treated patients, but high-risk groups such as the elderly have substantially higher rates. Risk factors include age, female sex, affective disorders, and probably those without psychotic diagnoses, including patients receiving drugs with antidopaminergic activity for nausea or gastrointestinal dysfunction for extended periods. Total drug exposure is positively correlated with tardive dyskinesia risk. Management strategies include a careful evaluation of both the psychiatric and neurologic states, a broad differential diagnosis, and adjustment of neuroleptic agents to the lowest effective dose that controls psychosis and minimizes motor side effects. No drug therapy is uniformly safe and effective for treating this disorder. A favorable long-term outcome of improvement or resolution correlates with younger age, early detection, lower drug exposure, and duration of follow-up.

(Casey DE: Tardive dyskinesia. West J Med 1990 Nov; 153:535-541)

Tardive dyskinesia (TD) is a drug-induced syndrome of involuntary hyperkinetic abnormal movements that occur in predisposed persons during or after the cessation of long-term neuroleptic (antipsychotic) drug therapy. Although these agents are highly efficacious in controlling psychotic symptoms, concern regarding the possible irreversibility of TD has led to a reconsideration of the appropriate indications for neuroleptic drug use. The clinical challenge is to optimize the many benefits attainable with these agents and to minimize their risks. Tardive dyskinesia has stimulated much research into the desirable and undesirable mechanisms of action of these agents and has also fostered the pursuit of new neuroleptic drugs that both control psychosis and have no neurologic motor side effects.

Tardive dyskinesia was first described in 1957 in German by Schönecker,[1] and a second report appeared in 1959 in French.[2] The first English-language publication came from a group in Denmark in 1960.[3] During the next several years, other reports confirmed these original observations and variously labeled the syndrome as "bucco-linguo-masticatory syndrome," "terminal extrapyramidal insufficiency syndrome," and "tardive dyskinesia." The last phrase was coined in 1964 and remains in use today.[4] During the 1960s, there was a lively debate about whether TD existed as a separate entity; was a group of symptoms to be included in the already-recognized, early-onset, and fully reversible extrapyramidal syndrome of acute dystonia, drug-induced parkinsonism, or akathisia; or was associated with the underlying psychotic illness and unrelated to drug therapy. During the 1970s TD was recognized as a specific syndrome, and efforts primarily focused on characterizing the epidemiology and risk factors associated with it. In the 1980s, drugs for the treatment of TD were pursued and indications for the proper use of neuroleptic agents to prevent TD were developed.

Clinical Description

Tardive dyskinesia is characterized by repetitive, involuntary, purposeless movements. The typical signs include chewing; tongue protrusion; vermicular tongue activity; lip smacking, puckering, and pursing; or paroxysms of rapid eye blinking. Choreoathetoid movements in the limbs and trunk can also occur. Dyskinesias in the fingers may look as if the patient is playing an invisible guitar or piano. Very rarely TD produces aerophagia, irregular respiratory rates, and grunting noises.

Recent attention has focused on atypical or nonclassical forms of TD. Tardive dystonia is a syndrome of sustained abnormal postures or positions such as torticollis, blepharospasm, grimacing, and truncal torsion.[5] Tardive akathisia is a syndrome of persisting subjective or objective signs of restlessness.[6] Both these atypical disorders may occur alone, with typical signs of TD, or with the other acute extrapyramidal syndromes. It is unclear if these typical and atypical presentations of TD have distinctly different pathophysiologic mechanisms or if they are better explained by a single underlying pathophysiology that is phenomenologically expressed in varied symptom clusters.

Tardive dyskinesia can also occur in children. In some, there may be few orofacial dyskinesias and a predominance of limb and truncal symptoms; in others, TD is more similar to that typically found in adults.[7,8]

Terminology

Several descriptive and temporal aspects of the disorder apply to both clinical care and research. Covert TD refers to existing tardive dyskinesia that is unmasked when neuroleptic drug treatment is reduced or discontinued. Withdrawal TD appears under similar treatment conditions but disappears spontaneously in one to three months. Irreversible TD has been arbitrarily defined as that persisting be-

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ABBREVIATIONS USED IN TEXT

GABA = γ-aminobutyric acid
TD = tardive dyskinesia

yond 6 to 12 months. Such categorizing, however, unnecessarily conceptualizes the course of TD into too narrow a time frame and does not account for symptom resolution noted in many patients observed for several years. Recent terminology has therefore emphasized the concept of persisting versus resolving TD.[9] Although no specific pathophysiologic mechanism for each time course and outcome has been verified, the most plausible explanation is that these symptoms occur along a continuum ranging from reversible to irreversible.

Research criteria have also been established for characterizing TD.[10] These are at least three months of cumulative neuroleptic drug treatment, at least mild movements in two or more body areas or moderate dyskinesias in one, persistence of symptoms for three months or longer, and the absence of other conditions that produce involuntary hyperkinetic dyskinesias. The most commonly used rating tool for TD is the abnormal involuntary movement scale.[11] Although helpful in characterizing abnormal movements, rating scales are primarily used for descriptive purposes. They are not diagnostic instruments. Diagnoses require a complete analysis of epidemiologic, etiologic, and temporal aspects of any symptom constellation in conjunction with a thorough examination.

Differential Diagnosis

Abnormal involuntary movements have many causes and may occur spontaneously in idiopathic syndromes, arise from other drug treatments, may be associated with hereditary diseases, or may be part of systemic illnesses.

Idiopathic Syndromes

Long before the introduction of neuroleptic drugs, spontaneous hyperkinetic dyskinesias of "grimacing" and "irregular movements of tongue and lips" were described in psychotic patients, most notably when the current-day concepts of schizophrenia and manic-depressive illness were established by Kraepelin at the turn of this century and by Bleuler.[12-14]

Stereotypies (purposeless, meaningless actions) and mannerisms (peculiar ways of carrying out normal actions) of psychosis are part of a differential diagnosis of tardive dyskinesia. Syndromes now classified as focal dystonias were previously identified as "spontaneous orofacial dyskinesia," "senile dyskinesia," and "blepharospasm-oromandibular dystonia."[15] These dyskinesias (dystonias) occur increasingly with aging. It has also been noted that patients with underlying neuromedical conditions have higher rates of "spontaneous" involuntary dyskinesias when compared with healthy age-matched controls.[16] Tourette's syndrome is defined by involuntary tics and vocalizations. It begins in childhood and continues with a waxing and waning course throughout a patient's lifetime. Simple persisting tics in an isolated muscle group must also be differentiated from TD. Dental problems can also cause oral dyskinesias that look like this disorder.[17]

Neuroleptic Drug-induced Acute Extrapyramidal Syndrome

Neuroleptic drugs also produce an acute extrapyramidal syndrome that develops with the initiation of treatment and may continue throughout the course of drug therapy. The syndrome gradually resolves over a few days to weeks when neuroleptic therapy is discontinued. Because the acute extrapyramidal syndrome and tardive dyskinesia can coexist,[17,18] both disorders must be considered in the differential diagnosis. Acute dystonia is a syndrome of episodically sustained abnormal postures such as oculogyric crisis, torticollis, trismus, laryngopharyngeal spasm, and torsion of the limbs and trunk. It occurs most often during the first four days of drug therapy. Neuroleptic-induced parkinsonism of tremor, rigidity, or bradykinesia usually develops after several days or weeks of drug therapy. It is symptomatically identical to idiopathic parkinsonism. Akathisia is a syndrome of subjective feelings or objective signs of restlessness that may have motor manifestations of walking in place, continuous motions of the trunk, or an inability to sit still. The rabbit syndrome is an uncommon form of drug-induced parkinsonism characterized by rapid rhythmic tremors in the lips and perioral area.[19]

Paradoxic TD is a syndrome that is rarely reported but probably occurs more often. It is symptomatically similar to typical TD but is pharmacologically like acute extrapyramidal syndromes because it often reverses with antiextrapyramidal syndrome drug therapy.[17,20,21] Paradoxic tardive dyskinesia emphasizes the important point that different pathophysiologic mechanisms may be expressed clinically by a limited number of common pathways to produce similar symptoms, such as these hyperkinetic dyskinesias.

All acute extrapyramidal symptoms respond to antiextrapyramidal syndrome drugs, but tardive dyskinesia remains unchanged or worsens with their use. Some drugs commonly prescribed for extrapyramidal syndromes include the anticholinergic agents benztropine mesylate (Cogentin), biperiden (Akineton), procyclidine hydrochloride (Kemadrin), and trihexyphenidyl hydrochloride (Artane); the antihistaminic-anticholinergic diphenhydramine hydrochloride (Benadryl); and the prodopaminergic drug amantadine hydrochloride (Symmetrel).

Other Drug-induced Dyskinesias

Many other drugs can produce hyperkinetic movement disorders that must also be differentiated from TD.[17] Dopamine agonists such as bromocriptine mesylate and the dopamine precursor levodopa can produce hyperkinetic dyskinesias. The abuse of amphetamines and other stimulants can cause chorea and stereotyped behavior during both drug intoxication and withdrawal. Anticholinergic and antihistaminic agents have rarely been associated with orofacial dyskinesias. Several anticonvulsant agents can produce dyskinesias resembling TD when these drugs are taken either at or above therapeutic levels. Oral contraceptives and the chloroquine-based antimalarial agents can also cause chorea and other dyskinetic symptoms. Rarely, the use of benzodiazepines has been correlated with orofacial dyskinesias. Both lithium carbonate use and that of tricyclic antidepressants have been associated with aggravating existing TD. These agents can also produce rapid, fine, irregular tremors that may be superimposed on tardive dyskinesia. This brief list is not intended to exhaustively review all drug-related involuntary hyperkinetic dyskinesias. Rather, it identifies some of the more commonly prescribed drugs that need to be differentiated as causes of dyskinesias.

Hereditary and Systemic Illnesses

Hereditary neurologic diseases may provide a difficult differential diagnosis for tardive dyskinesia if patients have

also received previous neuroleptic drug treatment. Huntington's disease is characterized by choreoathetosis and dementia that may be preceded or accompanied by symptoms of psychosis. The family history, the progressive nature of the symptoms, and the development of dementia aid in the differential diagnosis. Wilson's disease (hepatolenticular degeneration), a disorder of copper metabolism, is also usually distinguishable by clinical signs, laboratory tests, and perhaps family history. As these patients are often treated with neuroleptic drugs, the eventual development of dyskinesias makes distinguishing between TD and hereditary neurologic disease difficult. Though rare, Hallervorden-Spatz disease of iron metabolism usually has its onset during childhood and is characterized by bradykinesia and dystonia. The dystonic symptoms of Hallervorden-Spatz disease make it necessary to distinguish this disorder from neuroleptic drug-induced tardive dystonia in children.

Hyperkinetic movement disorders are also part of the overall constellation of symptoms occurring in many illnesses or disturbances in normal physiologic mechanisms. Endocrinopathies of hyperthyroidism, hypoparathyroidism, or hyperglycemia are infrequently associated with choreoathetosis. Chorea in pregnancy, known as chorea gravidarum, may possibly share some pathophysiologic mechanisms in common with oral contraceptive-induced chorea. Dyskinesias associated with the immune syndromes of lupus erythematosus, Schönlein-Henoch purpura, and Sydenham's chorea—as well as encephalitis or other inflammatory diseases of the central nervous system—must likewise be distinguished from TD.[17]

Epidemiology

The prevalence (number of existing cases) of tardive dyskinesia varies widely, ranging from 0.5% to more than 70%.[9,14,22,23] This broad range reflects the relative contributions of many different variables, including special populations at risk, past and current drug treatment, strictness of criteria for diagnosis, and the publication year. Realistic rates of TD prevalence average from 15% to 20%. They may, however, exceed 50% in high-risk populations such as elderly persons with long-standing psychosis, several decades of neuroleptic treatment, and confounding neuromedical conditions such as dementia.

To account accurately for those patients with spontaneous dyskinesias who would have eventually presented with abnormal involuntary dyskinesias even if no neuroleptic drug treatment had ever been prescribed, we must reduce the approximate TD prevalence rate of 20% by the 1% to 5% prevalence rate for naturally occurring spontaneous dyskinesias, as described earlier.

Schizophrenia develops in about 1% (2.5 million) of the population (250 million), and most are treated with neuroleptic agents. Tardive dyskinesia develops in 14% (350,000) of these patients. Add to this the substantial number of demented and behaviorally disturbed persons receiving neuroleptic drugs, and the actual prevalence of the syndrome is evident.

The incidence (new cases per year) of TD is about 3% to 5%.[24-27] Because prevalence studies reflect the number of patients at a single cross-sectional point in time, these numbers do not account for the addition of new cases and the subtraction of those that have resolved. Although long-term outcome data are just now becoming available, it seems that the relatively stable prevalence rate of 15% to 20% reflects a considerable turnover in affected cases because about as many cases resolve as new ones develop.[27]

Risk Factors

Age and Sex

The prevalence of tardive dyskinesia steadily increases with age. It occurs in 5% to 10% of patients younger than 40 and rises to a range of 50% to 70% in patients older than 65.[9,28] Most but not all studies show that TD occurs more often in women at an approximate ratio of 1.7 to 1.[9,22,23]

Psychiatric Diagnosis

The vulnerability to tardive dyskinesia may be greatly influenced by psychiatric diagnosis. It is not known why more severe TD develops in patients with affective disorders, particularly depression, and it does so after relatively brief exposures to low doses of neuroleptic drugs.[29,30] This implies that patients with schizophrenia may be relatively less vulnerable to TD.[31]

Persons without psychotic diagnoses who receive extended treatment with neuroleptic agents are also at substantial risk for TD development. Included are those patients receiving long-term treatment with antiemetic drugs such as prochlorperazine (Compazine) and others or with the widely used compound metoclopramide hydrochloride (Reglan). Although metoclopramide hydrochloride is marketed for gastrointestinal disorders and nausea, its mechanism of action—like that of antiemetics and all neuroleptics agents—is through dopamine-receptor blockade. Metoclopramide has antipsychotic effects at higher doses and can produce all the acute extrapyramidal symptoms and TD from the doses commonly prescribed for gastrointestinal disorders.[32] While there is relatively little risk of inducing TD with a short-term course (about four weeks or less) of antiemetics or metoclopramide, this risk increases steadily with extended treatment. It is essential to periodically reassess the need for these drugs when their use is long term to ensure that the risk-benefit ratio remains favorable.

Neuroleptic Dose and Duration of Treatment

The relationship between TD and drug treatment variables is complex. A large, long-term, prospective study of tardive dyskinesia shows a significant positive correlation between its onset and both total treatment duration and total drug dose.[24] No studies have yet teased apart the complex interaction between concomitantly increasing age and total duration of treatment.

Prospective studies correlating blood levels of neuroleptic agents with tardive dyskinesia have not yet been done. In cross-sectional evaluations, blood levels of these drugs were higher in patients with TD than in those without the disorder in one study, but this was not confirmed in a subsequent investigation.[33,34]

Neuroleptic Drug Type

While it has been occasionally claimed that one drug or particular characteristics of certain drugs (for example, a specific chemical class, high versus low doses, receptor-site specificity) are associated with a greater or lesser risk of tardive dyskinesia, the widely conflicting findings across studies do not sufficiently resolve this issue. The proposal that long-acting neuroleptic agents are associated with a greater risk of TD is also highly questionable because of difficulties in interpreting the pharmacologic consequences of treatment with injectable depot drugs that may have

different rates and amounts of drug absorption compared with oral agents. At present, an objective evaluation of the data must conclude that the commercially available neuroleptic drugs appear more similar than different (with the probable exception of clozapine) and that it is impossible to implicate one drug or drug class as more or less liable to produce TD.

Clozapine (Clozaril), whose mechanism of action is unknown, is the best example of an atypical neuroleptic agent. Although it has weak dopamine-receptor antagonist properties, it has more potent antagonistic activity at several other neurotransmitter sites—serotonergic, cholinergic, histaminic, α-adrenergic. Clozapine produces exceptionally low rates of acute extrapyramidal syndromes, and there are no well-documented cases of TD from extended clozapine use.[35] The effect of clozapine on tardive dyskinesia is highly variable. In some patients the drug suppresses the syndrome while in others it has no effect.[35] Because experience with clozapine is still limited, it is too early to draw firm conclusions about the liability of clozapine to produce TD. The risk of agranulocytosis (1% to 2%) and the limited indication for use in treatment-resistant schizophrenia make clozapine a second line of drug therapy reserved for special situations.

Drug-free Periods

Time off neuroleptic agents ("drug holiday") has the advantage of reducing drug exposure, unmasking covert dyskinesias, and evaluating if the drug therapy is still required. On the other hand, such time off exposes patients to the risk of a psychotic relapse. The most appropriate strategy is to gradually decrease the dose to the lowest effective level. Some patients show signs of impending psychotic relapse before the drug can be discontinued. In these patients, continuing the drug dose at the previous effective level is recommended. For other persons neuroleptic agents can gradually be reduced to much lower levels and possibly even discontinued. In this case, patients should remain off neuroleptic therapy as long as possible. It is still unclear whether periodic drug holidays are associated with higher rates of irreversible TD, as has been suggested.[36]

Anticholinergic Drugs and the Extrapyramidal Syndrome

The etiologic role of anticholinergic drugs in tardive dyskinesia is disputed. Data exist both for and against a correlation with TD risk.[22,23] In contrast to the controversial etiologic role, it is consistently shown that anticholinergic agents may temporarily aggravate existing TD, but the symptoms return to baseline when these drugs are discontinued.[20-22,37]

The acute extrapyramidal syndromes have been hypothesized as a risk factor for TD.[38] In a prospective study of tardive dyskinesia, parkinsonian side effects significantly correlated with the early (defined as less than a year of drug treatment) onset of TD but were not associated with TD of a later onset.[39] Why such a risk factor would be evident in the first year of treatment and not thereafter is unclear. Clarifying the relationship between TD and acute extrapyramidal symptoms is very difficult because these symptoms are multidetermined. Patient (age, sex, psychiatric diagnosis), drug (dose, type, duration) factors, and the presence or absence of agents that prevent extrapyramidal symptoms may alter the vulnerability to this disorder.[40,41] Because anticholinergic drugs are used to treat extrapyramidal symptoms, the retrospective associations between tardive dyskinesia and anticholinergic agents may actually represent indirect measures of the correlation between acute extrapyramidal symptoms and late TD risk.

Organic Brain Factors

Organic brain disease was identified as a risk factor in the early TD studies, but subsequent reviews questioned these associations.[22,23] Computed tomographic studies have also produced conflicting findings.[42,43] Several methodologic problems—such as lack of age-matched controls, confounding effects of masked symptoms from concurrent neuroleptic drug treatment, and lack of standardized measurement techniques—all may have contributed to these inconsistent results. Despite the lack of consensus about the associations between brain disease and tardive dyskinesia, there is face validity to the rationale that preexisting deficits enhance the vulnerability to other dysfunctions in the same system.

Management Strategies

Prevention of tardive dyskinesia is the best strategy because there is no uniformly safe and effective treatment of this syndrome. Although some researchers have strongly admonished against using neuroleptic drugs in any patient with TD, this is not practical as it leads to the unacceptable consequences of denying highly beneficial treatment to psychotic patients. The central question is how to provide appropriate neuroleptic drug treatment and at the same time minimize treatment risks (Figure 1).[44] The same strategy is used to manage patients with and those without TD. Physicians should have a high index of suspicion and keep a vigilant watch for the early beginning or worsening of TD symptoms. If they develop, a thorough differential diagnosis and treatment strategies should be considered.

As in all other branches of medicine, informed consent is

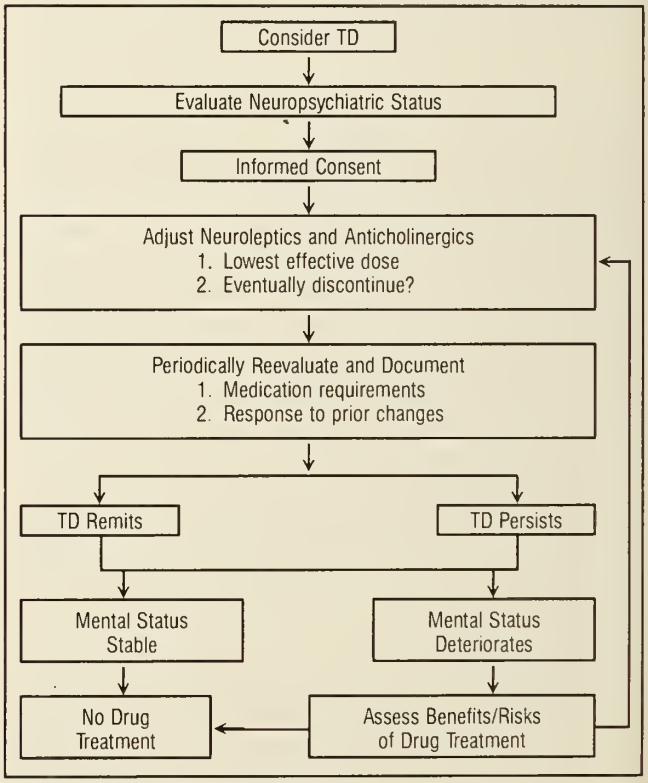

Figure 1.—An algorithm has been developed for managing tardive dyskinesia (TD) (adapted and reprinted by permission of the publisher from Casey and Gerlach,[44] Figure 2, page 184).

an important aspect of neuroleptic drug use and TD. The risks and benefits of treatment, alternative treatments, and no treatment should be discussed with patients and, if possible, a concerned family member or friend and should be documented. This best occurs when patients can understand the information and should be done whether or not TD is present. It is useful to periodically review this information with patients during long-term care. Informed consent is more of a process that occurs over time than it is a ritualized signing of a form as a one-time event.

The American Psychiatric Association Task Force on Late Neurological Effects of Antipsychotic Drugs advocates using neuroleptic agents in the lowest effective dose for only those patients who benefit from therapy.[22] Neuroleptic drugs are primarily indicated for acute and chronic schizophrenia and other uncommon neurologic disorders such as Tourette's syndrome and Huntington's disease. Secondary indications include acute mania or psychotic depression. Extended use may be justified with unstable manic-depressive illness where patients have failed to benefit from lithium or carbamazepine. Neuroleptic agents are not indicated for neurosis, personality disorders, insomnia, or other nonpsychotic conditions.

It is important to adjust periodically to the lowest effective level the doses of neuroleptic drugs and those preventing extrapyramidal symptoms. Some patients can eventually discontinue these agents, but others must maintain therapy to prevent an exacerbation of psychosis. Regularly reevaluating medication requirements and benefits, discussing them with patients and their families, and documenting such efforts should be established principles of practice.

Tardive dyskinesia either persists or gradually remits. The mental state may remain stable or deteriorate with an exacerbation of psychosis. When such a relapse occurs, it is necessary to reassess the risks and benefits of treatment with neuroleptic agents as was done when it was started and then reevaluated at each medication adjustment.

Long-term Outcome

The possibility of a reversible course of tardive dyskinesia, even in patients continuing on neuroleptic agents, has been noted since the earliest reports.[1-3] This favorable outcome is not well known, though, because it has been overshadowed by the reports that TD may not resolve.

Improvement across studies varies from 0% to 92%.[9,26,45] This wide range is due to the multiple factors of patient variables (for example, age), treatment variables (drug dose and cumulative exposure), and temporal aspects (early diagnosis, duration of treatment, and duration of TD follow-up). Age is consistently correlated with improvement in tardive dyskinesia: Younger patients are more likely to improve.[9,26,28] Nevertheless, this does not exclude older patients from having improvement or resolution, as this favorable course can occur in any age group. Data are insufficient to clarify whether gender or psychiatric diagnosis correlates with TD outcome.

Early diagnosis is often but not always associated with a good prognosis, perhaps because most TD outcome studies are initiated after symptoms are identified, and it is impossible to know when symptoms first developed as long-standing covert TD may have been masked by neuroleptic therapy. One large prospective study shows that a favorable outcome correlates with less drug treatment,[46] although another study and a review of the subject noted that a uniformly good outcome is not predictable.[47]

The few studies specifically addressing TD outcome when neuroleptic therapy is continued also show that symptoms may stabilize, lessen, or resolve over many years. Only a few patients have increased TD during continued treatment with neuroleptic agents.[9,26] Overall, the longer the follow-up period, the better the outcome. The most important caveat, however, is that most outcome studies in patients remaining on neuroleptic therapy have evaluated the effects of these drugs only at low to moderate doses (for example, chlorpromazine equivalents of 600 mg or less per day). The effect of extended treatment in TD patients at doses above this level is unknown.

The recommendation for the lowest effective dose (which includes discontinuing neuroleptic agents if possible) may be questioned if some data suggest that TD does not worsen with continued drug therapy. Still, there are several reasons for this "less is better" strategy. First, if a lower dose does as well as a higher one, the lower dose is desirable because it is less likely to produce acute and long-term side effects. Second, this will lead to better compliance, as dose-related side effects are often the reason why patients discontinue taking medicines. Third and most important, some evidence suggests that patients not receiving neuroleptic drugs have better outcomes than those continuing to take these drugs.[46] This implies that these agents retard, but do not necessarily prohibit, the course of spontaneous remission. Thus, managing psychosis and tardive dyskinesia rests on a basic tenet of medicine: Use the lowest effective dose of drugs only in patients who benefit from them.

An intriguing but unexplainable question is how neuroleptic agents can cause TD, which then gradually abates or resolves even with continued treatment with the class of drugs that caused the initial symptoms. This raises the possibility that neuroleptic agents play only a partial role in the pathophysiology of TD, perhaps by converting a covert vulnerability to overt dyskinetic symptoms. It also challenges the commonly held view that the central nervous system cannot compensate for long-standing dysfunction.

Treatment

Treating tardive dyskinesia is a clinical challenge. Unfortunately, no drugs are uniformly safe and effective over extended treatment periods. The long list of the many drugs used to study TD attests to their general lack of therapeutic benefits. Depending on one's perspective, there are many treatments for TD or there are none.[9,37]

Several assessments are frequently necessary to accurately account for the masking and unmasking effects of drug treatment. Without the opportunity to follow symptoms over time, it is possible to develop misleading impressions about the course of tardive dyskinesia. For example, the disorder may appear to emerge or worsen when the drug dosage is decreased because symptoms are unmasked. This unmasking could also occur when anticholinergic agents are added. Similarly, TD symptoms may appear to lessen or resolve when the neuroleptic drug dose is increased or when anticholinergic agents are decreased because symptoms are masked.

Dopamine

Reducing dopaminergic function is the most effective way of suppressing (masking) tardive dyskinesia. Yet this strategy, when used solely to suppress TD, is justified only in those rare cases when TD is severe, debilitating, or life-threatening. Functional reduction of dopamine can be

achieved with presynaptic depletion (reserpine) or by false transmission (methyldopa [Aldomet]) but yields only variably beneficial effects.[22,37] Although reserpine has rarely if ever been associated with causing TD, it and other drugs that decrease catecholamine function should be used cautiously because of the theoretic possibility that this approach, like the use of neuroleptic agents, reproduces the same biochemical pathophysiology as dopamine-receptor blockade. In addition, these drugs have their own undesirable and potentially troublesome side effects.

The theoretically attractive approach of resetting dopaminergic hypersensitivity back to normal sensitivity with dopamine agonists (bromocriptine mesylate [Parlodel]) or dopamine precursors (levodopa) has not been consistently successful. As with so many other treatment trials of TD, the initial positive results have not been replicated in subsequent investigations.[9,22,37]

Acetylcholine

Anticholinergic agents usually aggravate existing tardive dyskinesia or unmask covert TD. Rarely, they seem to be beneficial in TD-like hyperkinetic dyskinesias but are probably treating the uncommon syndrome of paradoxic TD (see Differential Diagnosis).

Another theoretically attractive approach to treating TD was to augment the cholinergic system with the cholinesterase inhibitor physostigmine or through dietary cholinergic-precursor loading. Trials with physostigmine have been inconsistent, and the lack of a widely available oral form makes its use impractical. Dietary approaches with choline or lecithin (PhosChol) were again initially encouraging but subsequently disappointing.[9,22,37]

Other Drugs

Compounds aimed at enhancing γ-aminobutyric acid (GABA) activity, either through direct agonism or by inhibiting the catalytic enzyme GABA-transaminase, all have produced inconsistent results. Preparations such as baclofen (Lioresal) and sodium valproate (Depakene)—with mechanisms of action that may or may not be related to GABA function—have not been consistently effective and are not recommended for routine use.

Benzodiazepines often temporarily reduce TD but rarely may aggravate it. The nonspecific sedative effects of these drugs may be their main benefit. Although diazepam may provide symptomatic relief of TD, it is not routinely recommended because of the potential problems with dependence during extended use.

Other drugs that have been generally ineffective include the serotonergic agent, tryptophan, and cyproheptadine hydrochloride (Periactin); the noradrenergic agents such as lithium carbonate (Lithane, Eskalith); the β-adrenergic receptor antagonist propranolol hydrochloride (Inderal); and the α-adrenergic agonist clonidine hydrochloride (Catapres). Studies that have more theoretic implication than practical application and that have also failed to yield convincingly positive results include the neuropeptides met-enkephalin, destyrosine-γ-endorphin, vasopressin, and approaches through the opiate system with morphine and naloxone hydrochloride (Narcan). In addition, trials with estrogen, pyridoxine, fusaric acid, manganese chloride, phenytoin (Dilantin), ergoloid mesylates (Hydergine), papaverine hydrochloride, and several others have produced no or only sporadic benefits.[9,22,37] While the results of these many varied trials are generally not encouraging, it may be worthwhile considering one of these therapeutic approaches if TD symptoms are severe and there are no indications for the appropriate use of neuroleptic agents.

Much has been learned about tardive dyskinesia in recent years, but much more needs to be unraveled. It is thus appropriate to retain an open view on all aspects of this syndrome. Developing new drugs that treat psychosis and do not bring on tardive dyskinesia or extrapyramidal symptoms is a priority of researchers. Achieving this goal will be a major breakthrough both in patient care and knowledge about the mechanisms underlying psychosis.

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WALKING THE QUILT

(The NAMES PROJECT, AIDS Quilt)

incomprehensible size does not cauterize;
this room throbs with unreprieved tales
of harbors and streets, palettes and boots
related to an emptiness that names itself

- this purple slash riots like laughter
- along the careful names I carefully read
- unknowing yet kin-known through and through—
- gilt could not mean more

this is a beachwalking among the dead
full of wise driftwood and sudden wind,
memory without decay, sunset sans romance,
the accompaniment of one's need to know

- musical notes plummet down the sewn edge
- where this devotee of blues forever meets
- a benefactor of rainbows, such smiles
- one would grope blind alleys to find

tissue boxes bespeak the common round;
these silent, gentle faces freely give
like abolished forests creating their last air
before the saw's undebatable limitation

- sometimes something scarlet beaks forward
- across panels of mesmeric sorrow;
- I founder as in a valley whose mountains
- have wept their entire faces all down

helpers dressed in reality patiently groundskeep
the long rows shockingly cruciform,
attention's punctuation marking the ways
every one of us came together here

- teddybears and glitter, denim and books,
- the told lives irreducibly braved, these panels
- I walk my sisterhood along, distance and memory
- joined with unimpeachable love

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Epitomes

Important Advances in Clinical Medicine

Neurosurgery

The Scientific Board of the California Medical Association presents the following inventory of items of progress in neurosurgery. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers, or scholars to stay abreast of these items of progress in neurosurgery that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Neurosurgery of the California Medical Association, and the summaries were prepared under its direction.

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Brachial Plexus Birth Injury

THE FIRST EXPERIENCES with brachial plexus exploration in the infant were reported 85 years ago, in which gratifying functional recoveries occurred after the direct suture of ruptured upper plexus elements. Because surgical and anesthetic techniques were relatively primitive, only a few surgeons achieved consistent, satisfactory results, and by the mid-1920s, surgical attention had shifted from the reanimation of paralyzed muscle groups to mitigating the skeletal consequences of paralysis, contracture, and joint deformity.

Two major developments have revived the practice of brachial plexus exploration for infants with birth injuries. The first is a refinement of the peripheral nerve microsurgical procedures and pediatric anesthesia that has made long procedures to reconstruct miniature infant brachial plexuses both feasible and safe. The second is a recent clarification of the natural history of plexus birth injury that has shed invaluable light on the process of patient selection.

Between 75% and 95% of newborns with brachial plexus palsies will make complete, spontaneous recoveries. Identifying the minority who are destined to a degree of functional disability that might justify surgical intervention has been problematic. Initial flaccidity of the entire limb without any movements of the fingers or wrist has long been recognized as an adverse prognostic sign, as has the presence of Horner's syndrome. In the late 1970s the precision of early prognostication was advanced when the rates of recovery in a cohort of conservatively managed neonates were prospectively examined. Observations were distilled into the following succinct clinical rule: If perceptible muscle contractions have not returned to the deltoid and the biceps by the end of the third month, the ultimate functional recovery of the shoulder and the arm will be unsatisfactory.

This rule, which has been corroborated by several subsequent investigations, has encouraged the application of modern peripheral nerve microsurgical techniques to brachial plexus birth injuries. The most practical goal has been to reanimate the muscles supplied by the upper trunk: the abductors and external rotators of the shoulder and the flexors of the elbow. The most common pattern of injury, neuromata involving the C-5 and C-6 spinal nerves and the upper trunk, has been managed by excision and reconstruction with sural nerve grafts. In less common cases, when the C-5 and C-6 nerves have not been suitable for reconstruction because of intraforaminal injuries or avulsion from the spinal cord, distal upper plexus elements have been neurotized by using the intercostal nerves, the spinal accessory nerve, and other sources of motor outflow.

Surgical groups from Europe, Scandinavia, and the United States have reported gratifying clinical results. The largest experience has been 178 surgical cases reported from Paris. On the basis of previous natural history data, the researchers explored the plexuses of infants shortly after 3 months of age if there was no sign of recovery in the deltoid and biceps muscles by that point. Although brachial plexus reconstruction does not produce normal limbs, long-term results indicate that operative intervention generally improves on the natural history by one clinical grade. Morbidity has been minimal. Whether plexus exploration is of benefit in older infants and children is not clear.

Even under the best of circumstances, in the two- or three-year interval required for the results of plexus reconstruction to become apparent, infants may need the services of a developmental pediatrician, a physiatrist, an orthopedic surgeon, and physical and occupational therapists. The neurosurgical management of plexus injury should be one part of a comprehensive program, and a prototypic multidisciplinary clinic has been described.

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Piatt JH Jr, Hudson AR, Hoffman HJ: Preliminary experiences with brachial plexus exploration in children: Birth injury and vehicular trauma. Neurosurgery 1988; 22:715-723

Endovascular Therapy for Intracranial Vascular Lesions

RECENT REPORTS HAVE SUGGESTED that various cerebrovascular lesions including intracranial aneurysms, vascular malformations, and vasospasm following subarachnoid hemorrhage can be treated successfully with interventional neuroradiologic techniques. Patients undergoing such endovascular therapy are often considered to be poor surgical risks or those in whom conventional neurosurgical tech-

niques have failed. These endovascular methods usually employ a transfemoral approach using local anesthesia and mild sedation. Intravascular catheters are guided into the intracranial circulation under direct fluoroscopic control. Detachable balloons may be placed in aneurysms or proximal vessels; various particles, thrombogenic coils, or glue may be injected into vascular malformations; or cerebral arteries narrowed by vasospasm may be dilated with microballoons. At present, these relatively new techniques have potential advantages but some limitations.

For difficult intracranial aneurysms, or for patients in poor medical or neurologic conditions, endovascular balloon occlusion of an aneurysm or feeding artery offers several benefits: an open craniotomy with general anesthesia and brain retraction is avoided; the patient's neurologic condition can be continually monitored during the procedure, and if the test occlusion is not tolerated, the balloon can be deflated; and an immediate, high-quality angiogram can be done following the balloon placement to verify the completeness of the occlusion and the patency of normal vessels. Serious pitfalls include immediate or delayed aneurysmal rupture due to subtotal occlusion and incomplete aneurysmal thrombosis; balloon rupture or balloon migration leading to hemorrhage or ischemic complications, especially in giant aneurysms wherein more than one balloon is required; persistent mass effect of the inflated balloons, even after aneurysmal thrombosis; and occlusion of the origins of perforators that are not angiographically visualized. Long-term follow-up in patients undergoing these procedures is still being conducted. Further research to find a safer endovascular therapy for difficult aneurysms is clearly warranted, and we are currently investigating the use of retrievable thrombogenic coils.

Endovascular embolization of intracranial vascular malformations is proving to be extremely valuable, usually as an adjunct to conventional microsurgical or radiosurgical procedures. Advantages include awake monitoring of patients with test injections of amobarbital sodium before definitive embolization; the ability to obliterate deep feeders or components of arteriovenous malformations (AVMs) that are surgically difficult; and the ability to stage the obliteration of large malformations, potentially allowing for the gradual return to normal of markedly altered hemodynamics. For large AVMs, we have recently been using embolization to reduce the nidus size before a radiosurgical procedure in an attempt to increase the obliteration rate and decrease the incidence of complications. In 45 patients receiving this combined therapy, the results are encouraging, although long-term follow-up is still needed. In select cases, such as carotid-cavernous fistulas, dural AVMs, vein of Galen aneurysms, and occasional parenchymal AVMs, endovascular treatment results in complete angiographic obliteration of the lesion. Limitations include the risk of inducing hemorrhage or infarction, either immediate or delayed; the small incidence of venous sinus thrombosis if a transvenous approach is used; and the possibility of AVM recanalization if the malformation is not removed. It is rare to obliterate completely a parenchymal AVM with endovascular treatment alone.

Balloon angioplasty for symptomatic vasospasm following subarachnoid hemorrhage is being attempted in specialized neurosurgical centers. Because delayed ischemic deterioration from vasospasm is still a major problem despite the use of hypervolemic, hypertensive therapy and systemic calcium antagonists, balloon angioplasty could have substantial therapeutic potential. Problems associated with the method include aneurysmal rupture if its neck has not been secured; a failure to improve the neurologic condition if unrecognized infarction has already occurred; the risk of inducing hemorrhage in an infarcted territory; and difficulty gaining access to the narrowest (often most symptomatic) arteries, smaller arterial branches, and perforators. The long-term side effects of intracranial angioplasty are also not known.

Endovascular therapy for cerebrovascular disorders has already made a major positive contribution. At present it still has certain limitations and does not replace open microsurgical techniques for patients in good condition with accessible lesions. With further technical advances and improvements in patient selection criteria, its role will undoubtedly be expanded and become better defined.

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Implanting Fetal Tissue to Treat Parkinson's Disease

THE CONCEPT OF RESTORING NEUROLOGIC function by transplanting neural tissue is old. A clear demonstration of its feasibility, however, came in 1979 with the publication of two important studies. In both, the researchers partially reversed the behavioral abnormalities seen in rats with pharmacologically induced nigrostriatal lesions by transplanting fetal tissue into the brain. The clinical implications for Parkinson's disease are clear. The motor disturbances seen in patients with Parkinson's disease primarily result from the loss of dopaminergic neurons in the pars compacta of the substantia nigra. These neurons project to the striatum where the release of dopamine from synaptic vesicles modulates motor function. The systemic delivery of levodopa dramatically improves function in these patients, but the results are far from ideal. The local production of dopamine in the striatum by transplanted tissue holds the promise of even greater clinical improvement.

In the initial attempts at transplantation in humans, autologous adrenal tissue was used as the source for dopamine. At best, the results have been limited and transient. The mechanism underlying the observed improvements is not known, but autopsy studies and research in animals strongly suggest that the release of catecholamines by viable graft cells is not a factor. The bulk of the data obtained from studies of animals over the past ten years indicates that fetal brain tissue is superior to adrenal tissue for this purpose. In 1987 a Scandinavian team did the first implantation of fetal mesencephalic cells into the human striatum. Perhaps as many as 100 similar procedures have been performed throughout the world to date, although documentation in the English-language literature has been scarce. Eight fetal cell implantations have been done in this country. The first of these has been described in detail: that

one patient has shown considerable improvement in motor function, sustained at one year. The degree of improvement mirrors that seen with the third patient in the Scandinavian series, as reported recently in *Science*. Positron emission tomographic scans using G-L-[^{18}F]fluorodopa in these patients suggest that viable graft cells are producing dopamine within the striatum.

Neural transplantation is in its infancy. The optimal age at which the embryonic tissue should be harvested is reasonably clear, but the method of delivery, the number of cells implanted, the exact target within the striatum, unilateral versus bilateral transplants, the immunologic factors at play, and the use of growth factors are but some of the issues that still need to be more thoroughly addressed. We are clearly on the verge of a new era in which the restoration of function within the central nervous system will be commonplace.

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Endoscopic Neurosurgery

IMAGE-DIRECTED STEREOTACTIC METHODS have enabled the safe and precise placement of endoscopes into the brain. The miniaturization of endoscopic instruments has enabled the development of smaller-diameter endoscopes, which minimizes the disruption of normal brain in approaching deep lesions. Miniaturization and technical improvements have occurred in optics (rigid as well as fiberoptic systems), operating instruments (rigid and flexible microforceps), continuous suction and irrigation systems, and fiber systems for delivering laser energy. In addition, intraoperative ultrasonography through a burr hole allows real-time monitoring of intracranial contents.

Endoscopic systems have now been used in numerous situations with relatively low complication rates, including the aspiration of colloid cysts of the third ventricle, biopsy and resection of cystic and intraventricular tumors, the evacuation of intracerebral hematomas, and a terminal-third ventriculostomy through a foramen of Monroe for hydrocephalus in patients with aqueductal stenosis or pineal region tumors.

A recent series reported on 109 endoscopic procedures for the evacuation of hematomas and 24 for biopsy and subtotal resection of a variety of intracranial tumors. Surgical morbidity was approximately 4% in the patients with intracranial hemorrhage and negligible in the patients with tumors.

Whether the endoscopic treatment of such lesions can be more effective than conventional management remains to be demonstrated, but certainly such procedures can be carried out with a high degree of safety due to the precision of localizing techniques and minimal invasiveness of the endoscopic instruments.

With advances in endoscopic technology, surgical instrumentation, and energy delivery (laser), endoscopic neurosurgical techniques may become increasingly important in the management of a variety of intracranial disorders.

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Indications for Stabilization in the Management of Lumbar Disc Disease

THE DIAGNOSIS OF MECHANICAL INSTABILITY of the lumbar spine is difficult to make with certainty and frequently is a diagnosis of exclusion. Practitioners caring for patients with degenerative lumbar disc disease must never forget the anatomy of the back, the important stabilizing role of the ligaments, facet joints, facet capsules, and musculature, and the important anatomic relationship of the disc to the intervertebral foramina. Any patient who has had a previous back operation, especially for the removal of a degenerative disc, may have instability at the operative level. This is especially true at the L4-5 level, which is the most mobile of the lumbar spine. A number of patients in whom the "failed back syndrome" develops after disc excision are suffering from excessive mobility at a motion segment(s) and will benefit from a stabilization procedure; the trick is to identify those patients in whom further surgical intervention is likely to be beneficial.

Most patients who have mechanical instability of the spine will have both back and leg pain, but the back pain is predominant. On physical examination, they will have impressive muscle spasm of the paravertebral musculature and be unwilling to move the back except with flexion at the hips. Plain lumbar spine films in flexion and extension may show excessive movement of the injured motion segment(s), there may be evidence of pseudospondylolisthesis, and unexpected iatrogenic pars and facet fractures are not infrequently identified. Magnetic resonance imaging or myelography usually is not impressively abnormal; there may be residual scarring or mild disc bulging, but in most of these patients large structural lesions are absent. The best preoperative predictor of whether a particular patient will benefit from a fusion is the response to a trial of immobilization in an acrylic body jacket. This jacket cannot be removed and is left on for four to six weeks. Patients who will benefit from fusion are able to reduce substantially their requirement for medication, often become pain-free in the jacket, and will have fairly prompt recurrence of significant back pain when the jacket is removed and replaced with a rigid but removable brace.

A fusion operation can be accomplished by a number of techniques with and without instrumentation and with both anterior and posterior approaches. The basic key to obtaining a solid fusion is bone bridging across the area of motion. Instrumented fusions without adequate bone or proper attention to preparing the fusion bed will ultimately fail because the initial stability provided by the instrumentation is lost as the metal parts loosen with continued motion over time.

Because spinal fusion for patients with the failed-back syndrome carries no guarantee that symptoms will be ameliorated, patients should be considered as candidates for

this procedure only after conservative measures of pain control have been completely exhausted. In addition, patients who are overweight should lose excess weight and participate in a spine muscle strengthening and flexibility program before being considered as candidates for a fusion procedure. In a certain number of well-motivated patients, dedicated efforts directed at weight control, muscle strengthening, and maintenance of proper spinal alignment and body mechanics can obviate the need for a large surgical procedure. In the right patients, however, a fusion procedure for mechanical instability of the lumbar spine can make the difference between disability and a meaningful life.

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Implantable Neurosurgical Drug Delivery Systems

IMPLANTABLE NEUROSURGICAL DEVICES provide an elegant and novel means of delivering drugs to the central nervous system. They have had increasing applications in the management of intractable pain, certain neurologic disorders, and malignant lesions and infections of the central nervous system.

The epidural, subarachnoid, or intraventricular administration of medication represents an effective approach to the delivery of drugs to a specific site within the central nervous system. This approach provides for a controlled, direct, and precise delivery of drugs. The identification of opiate receptors in the central nervous system stimulated the development of a method assuring the direct delivery of synthetic and semisynthetic opioids to the brain and spinal cord. By circumventing the blood-brain barrier, smaller dosages of medication are feasible and systemic side effects are minimized.

Implantable devices consisting of reservoirs and pumps are gaining increasing favor in neurosurgical practice. The surgical implantation of such devices is reasonably safe and easy. Catheters are placed in either the spinal epidural space or the subarachnoid space through a small skin incision or inside the cerebral ventricles through a small twist-drill hole. These catheters are then tunneled subcutaneously and connected to an infusion pump that is placed in a subcutaneous pocket, generally in the abdomen, flank, or chest. Such a closed system provides the advantages of long-term, controlled, sustained delivery of medication with minimal inconvenience and risk of infection.

Rapid technologic advances have provided sophisticated delivery systems. Large reservoirs filled percutaneously and placed remote from the delivery sites permit conveniently long intervals between drug refills, thereby minimizing the risk of infection, discomfort, and other complications. Remote programmable pumps permit changes in drug dosage by telemetry.

The use of such systems has seen increasing acceptance in the treatment of intractable cancer pain, otherwise difficult to control by oral or parenteral medication. Lumbar or cervical spinal catheter placement is used for the treatment of truncal pain. The intraventricular administration of opioids is effective for head and neck pain. The use of such opioid drug delivery systems for chronic pain of benign origin has been attempted in certain centers, but such application remains controversial. Furthermore, because these systems are expensive, they probably are not justified for short-term use.

Similar drug delivery systems have been used to good advantage in the treatment of malignant tumors and infections of the central nervous system. The intrathecal administration of baclofen for spasticity has received recent attention. Other neurologic disorders undoubtedly will be treated in a similar manner.

The long-term use of implantable drug delivery systems can result in a number of complications. Blocked or migrating catheters and pump failure are easily recognized and generally readily corrected. The development of drug tolerance is a more serious problem. Although this often represents a "pseudotolerance" resulting from a mechanical system failure, such tolerance to opioid medications may occur with long-term use. Generally drug tolerance develops more slowly with continuous spinal infusion than with bolus administration. The problem may be overcome initially by increasing the concentration or substituting another opioid. In intractable cases, however, narcotic detoxification may be necessary.

The direct delivery of medication to the central nervous system using implantable devices assures a controlled, sustained, convenient, and long-term administration of effective medication without compromising normal neurologic function and with minimal systemic side effects. This method should not be construed as a panacea. Proper patient selection is essential. Advancing technology offers an exciting prospect for benefiting future generations of patients through neurosurgical care.

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Interstitial Radiotherapy for Malignant Glioma

CURRENT THERAPY FOR MALIGNANT GLIOMA consisting of surgical resection, external-beam radiotherapy, and carmustine (BCNU) chemotherapy can prolong survival, but the overall prognosis remains poor. Most patients have significant tumor progression within the first two years after their initial treatment.

While the efficacy of external-beam radiotherapy in controlling residual tumor following surgical resection has been well established, increasing doses of radiation are associated with increasing toxicity to the surrounding brain. One strategy to deliver additional radiotherapy to the tumor has been to give a "boost" of radiation by implanting radioactive sources into the tumor bed. The theoretic advantages of such "seed implants" include a relatively high overall dose of radiation to the tumor with relatively low exposure to surrounding brain. Another possible advantage of tempo-

rary implants is the delivery of constant low-rate radiation that may enhance biologic effects on malignant cells.

During the past decade, the development of image-directed stereotactic systems has resulted in the ability to treat tumor volumes with radioactive sources (iodine 125 or iridium 192) with a high degree of accuracy and safety. Results from early trials of interstitial radiotherapy in selected patients have been encouraging, with quality survival as long as five years in a number of patients. Many neurosurgical centers are currently using this approach to treat malignant brain tumors (primary as well as metastatic) in conjunction with external-beam radiotherapy. Several groups have reported benefits of such treatment when compared with historical controls, but such effects in controlled studies remain to be quantified. Complication rates, both short and long term, also need to be better defined. Preliminary data suggest that short-term morbidity is less than 5%, but a number of patients require subsequent operations for recurrent masses. Posttreatment masses may include large volumes of necrotic tissue thought to result from the radiation implants. Because this is a relatively new form of treatment, long-term efficacy and complication rates also require further definition.

To summarize, interstitial radiotherapy is a logical adjuvant therapy in the management of malignant brain tumors. Initial data suggest efficacy in selected patients. Whether such therapy will become the standard of care will depend on the results of ongoing phase III investigations such as those of the Brain Tumor Cooperative Group. Randomized, controlled studies such as those of the Brain Tumor Cooperative Group hold the promise that the indications for and efficacy of interstitial radiotherapy will be determined.

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Management of Prolactin-Secreting Pituitary Adenomas

PROLACTIN-SECRETING ADENOMAS are the most common functioning pituitary tumors that present to clinicians. The successful integration of medical and surgical therapy provides an extremely high potential for the effective treatment of such tumors in terms of resolving endocrine symptoms and intracranial mass effects.

The medical treatment of prolactin-secreting pituitary tumors is based on the physiology of prolactin release—prolactin being the only hormone of the anterior pituitary to be regulated exclusively by a mechanism of tonic inhibition effected by neurotransmitter release from the hypothalamus. The neurotransmitter regulating the release of prolactin has dopaminergic characteristics, but whether it is dopamine is unknown. Bromocriptine, an ergot derivative with dopaminergic characteristics, effectively suppresses prolactin secretion and restores prolactin levels to normal in greater than 95% of patients with prolactin-secreting adenomas. It also significantly reduces the size of large prolactin-secreting tumors in at least 50% of patients and usually precludes further tumor growth once therapy is instituted. Bromocriptine therapy represents an acceptable alternative to surgical therapy, but the drug is not curative and not all patients tolerate its use. Furthermore, cessation of the drug results in a rapid return of hyperprolactinemia and the tumor reverts to at least its original size. Therefore, bromocriptine therapy is required for the lifetime of a patient when used alone.

Approaches to treatment involve a consideration of the stage of the tumor. Stage I lesions (less than 1 cm in diameter and confined to the intradural sella) are most amenable to surgical cure. The main indication for the treatment of such small lesions is patients' desire for pregnancy. The possible genesis of premature osteoporosis in women who are amenorrheic and hypoestrogenemic as a consequence of systemic hyperprolactinemia is a hypothetical concern that awaits clinical confirmation. In our experience, surgical resection of stage I lesions has an 84% chemical cure rate a year after resection, with morbidity less than 1% and mortality 0%. Serum prolactin levels measured six weeks postoperatively are used to determine whether further intervention is necessary. Bromocriptine therapy, on the other hand, restores normal serum prolactin levels in virtually 100% of patients who tolerate the drug, thus allowing normal pregnancy. Care must be taken with this approach, however, because tumor regrowth may necessitate reinstituting bromocriptine therapy during pregnancy. For stage I lesions, therefore, either surgical resection or bromocriptine therapy can effectively maximize the potential for pregnancy. The choice of therapy should depend on the patient's preference, taking into account the need for long-term medical management should an operation be deferred.

Stage II tumors (greater than 1 cm in size, with or without supraseller extension but without invasion of the dura or bone of the sella turcica) present similar treatment options, although the chemical cure rate of surgical treatment is only 50%, compared with 90% with bromocriptine use. Some stage II tumors, such as those that are cystic or of low density on a computed tomographic scan, generally do not shrink with bromocriptine therapy. This underlines the advantage of surgical resection in such cases—the reduction of tumor size.

Stage III tumors (local invasion of dura and sella) and stage IV tumors (diffuse sellar invasion with or without extension into the anterior, middle, or posterior fossa) defy cure by any single means. Surgical therapy alone achieves only a 25% physiologic cure of stage III lesions, and the physiologic cure of stage IV lesions approaches 0%. On the other hand, high doses of bromocriptine, with resulting increases in side effects, are required to have an effect on such large tumors. Therefore, we use combined therapy in stage III and IV tumors. The patient is initially placed on a regimen of increasing bromocriptine doses until a serum prolactin level of less than 20 ng per ml is established. If, after six weeks of normal prolactin levels, no reduction in tumor mass is observed on serial imaging studies, surgical resection is attempted. Imaging studies are done at three and nine months postoperatively and yearly thereafter. If postoperative imaging fails to show tumor progression and the prolactin level remains normal, no radiation therapy is given. Should the tumor progress despite bromocriptine therapy, radiation therapy is usually given. One indication for more urgent surgical intervention is progressive visual compromise despite bromocriptine therapy. Should significant reductions in tumor size be achieved with bromocriptine use, continued medical management becomes an op-

tion. In this case, yearly follow-up imaging studies are done to assess tumor status.

In summary, no single therapeutic modality is either ideal or unacceptable in the management of prolactin-secreting pituitary tumors. Fortunately, stage I and II tumors lend themselves to surgical cure, which avoids the need for a lifelong commitment to a medical regimen. The role of bromocriptine therapy adds a useful alternative to surgical intervention in some patients and also plays a crucial role in the combined management of more invasive lesions. The net result of this complementary set of therapeutic options is the reduction or elimination of tumor mass and the restoration of normal endocrine function.

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Surgical Treatment of Petroclival Meningiomas

There has been a dramatically increased interest in more aggressive surgical treatment of tumors at the base of the skull. New approaches are being developed, and old ones are being revitalized. Because of the complexity of the anatomy at the skull base, surgical approaches to this region are now frequently multidisciplinary, involving most often a neurosurgeon and an otolaryngologist. The team approach has provided tumor management that is more powerful than the sum of its parts, and nowhere is this more apparent than in the surgical treatment of meningiomas of the petrous bone and clivus, histologically benign lesions rendered malignant solely because of their relative surgical inaccessibility.

Petroclival meningiomas have been resected most commonly by the suboccipital (posterior fossa) retromastoid approach, and for most lesions this has been adequate. Surgical access to more complex lesions, however, such as those that extend to the prepontine cistern, middle fossa, or craniovertebral junction, require novel techniques often involving removing portions of the cranial base. Modern thinking stresses an approach that, while fundamentally a posterior fossa craniotomy, is different in that the sigmoid sinus is no longer the lateral limit to bone removal, such that a more direct line of vision along the petrous bone and in front of the cerebellum to the petrous apex and clivus is available to microsurgeons. This "petrosal" approach is now possible because the neurosurgery-neuro-otology team is not reluctant to drill anteriorly into the temporal bone.

There are three types of transpetrosal posterior fossa craniotomy: retrolabyrinthine, translabyrinthine, and transcochlear. In the retrolabyrinthine approach, bone removal anterior to the sigmoid sinus is halted at the level of the semicircular canals. Although this approach spares auditory function, it affords only a slightly improved access to the posterior fossa. In the translabyrinthine procedure, anterosigmoid bone is removed to the level of the internal auditory canal. This provides excellent visualization of the lateral aspect of the pons and upper medulla with only minimal retraction of the cerebellar hemisphere. Because the semicircular canals are removed, unilateral hearing loss is inevitable. In the transcochlear approach, the entire otic capsule is removed along with the middle ear and external auditory canal. By anteriorly rerouting the facial nerve from its intratemporal canal and then resecting both the petrous apex and lateral aspect of the clivus, an unimpeded view of the ventral aspect of the pons and clivus is obtained without the need for brain retraction. Hearing loss and transient facial palsy are acceptable deficits only with an otherwise inaccessible and potentially lethal tumor.

For tumors that arise high on the petrous bone and clivus, surgeons are adding a low temporal craniotomy to the petrosal approach with ligation of either the transverse or, more frequently, the superior petrosal sinus to allow splitting of the tentorium for additional superior exposure through the supratentorial space. For lesions arising from or extending to the low clivus or anterior rim of the foramen magnum, the lateral accentuation of the approach angle is gained by isolating and protecting the vertebral artery and drilling off the lateral aspect of the foramen magnum and occipital condyle. Because the sigmoid sinus sweeps anterosuperiorly at this level, drilling can be safely carried forward all the way to the hypoglossal canal. For these same low clival or anterior foramen magnum meningiomas, some surgeons are attempting an anterior (transoral, transclival) approach. Despite the development of fibrin glues for dural repair, however, the specter of postoperative cerebrospinal fluid leak into the oropharynx makes most surgeons reluctant to remove intradural lesions by this route.

Certain petroclival meningiomas will not be completely resectable despite the aforementioned advances in surgical access. For them, external radiation therapy, brachytherapy, and radiosurgery will be useful treatment adjuncts.

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Intraoperative Digital Subtraction Angiography for Neurosurgery

High-resolution, real-time, digital subtraction angiography (DSA) facilitates the intraoperative management of complex intracranial vascular disorders. Portable DSA equipment is now available that provides angiographic images virtually equivalent to conventional angiography. A mobile "C" arm fluoroscopy unit with high-resolution video is fitted with frame-averaging, catheter road mapping and automatic peak opacification capability. These features reduce the volume of contrast material necessary for adequate images. The system is powered by standard 115-volt, 20-ampere lines and requires no special shielding. The software package can be modified to allow for stereoscopic visualization of intracranial vascular lesions. Angiographic pictures accrue immediately, with the advantage of overlying bony and relatively radiopaque instrument subtraction. Carbon-fiber head holders can be subtracted, but ordinary metal instruments cannot. Draping, scalp hemostasis, and retraction require modification to avoid metallic artifacts. Technical considerations involved in intraoperative transfemoral or direct arterial catheterization have been described.

Indications for intraoperative neurosurgical DSA are di-

agnostic, therapeutic ("interventional"), or a combination of both. The obvious benefit of immediate intraoperative angiographic information is the ability to promptly and precisely improve therapeutic maneuvers. Arteriovenous malformations and fistulas, complex aneurysms, arterial occlusive disease, and hemorrhage localization compose the majority of lesions studied intraoperatively with DSA. The procedure does prolong operative time, so use is ordinarily reserved for more difficult intracranial vascular procedures. The incidence of technical surgical problems diagnosed by intraoperative angiography is significant. In one series, 7 of 32 procedures required intraoperative modification and in another series, 7 of 33. These relatively high rates are ascribable to the selection of difficult cases for treatment and study. The principal technical surgical problems detected include incomplete aneurysm clipping or arteriovenous malformation resection and unintentional vessel occlusion. These problems were corrected intraoperatively and confirmed by DSA. There have been no reports of major complications of DSA when the indications are clearly for diagnostic purposes.

Intraoperative DSA affords new options for treating inaccessible vascular lesions. Neurosurgeons can expose vessels otherwise inaccessible by catheter for the purpose of embolization, balloon occlusion, or angioplasty with the advantage of an immediate determination of the efficacy of the procedure. The progressively improving imaging capability of DSA, coupled with the mutual interests of neurosurgeons and neuroradiologists, is clearly resulting in an improved outcome for patients with difficult and challenging intracranial vascular disorders.

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Irritable Children

Acute irritability in a child is commonly due to an infection such as an upper or lower respiratory tract infection or gastroenteritis; a gastrointestinal disorder, such as a milk allergy or intolerance, appendicitis, intussusception or hernia; or trauma, especially inapparent fractures. Fever, dehydration, decreased food intake, pain, or sleep disturbances frequently worsen the degree of irritability. Chronic irritability may be due to a much broader range of pediatric illnesses that encompass chronic infection; endocrine and renal diseases; anemia, leukemia, and other such disorders; colic; parenting problems; neglect; abuse; and substance or toxin exposure. An overview of the common medical, surgical, and orthopedic causes of irritability is provided in several of the standard textbooks on pediatrics and critical care.

Emergency department physicians, family practitioners, or pediatricians, however, are confronted with other situations in which a child is irritable, yet no apparent reason can be determined. It is important, then, to realize that approximately 35% of children are seen in emergency departments because of neurologic problems. By considering the following, the need for further timely neurosurgical or neurologic consultation can be decided.

In general, a suspicion of central nervous system infection warrants an immediate evaluation that includes a lumbar puncture and, depending on the severity of symptoms, computed tomographic (CT) or magnetic resonance imaging (MRI) scanning and early antibiotic treatment. An irritable infant with a tense fontanel could have a subdural effusion, empyema, acute hydrocephalus, cerebral edema, or abscess, all of which require early and different neurologic and neurosurgical treatments.

Nonaccidental trauma from the shaking of infants is a frequent cause of unexplained irritability. A careful examination by a neurologist or neurosurgeon can detect retinal or subhyaloid hemorrhages, nuchal rigidity, hyperreflexia, and corticospinal tract involvement signaling the need for further diagnostic tests such as CT or MRI scanning and lumbar puncture. In a patient with multiple trauma with limited or no initial central nervous system symptoms, the later occurrence of irritability may not be related to systemic injury and pain. An evaluation to rule out an epidural, subdural, or subarachnoid hemorrhage should be considered. Mastoiditis can also result from a delayed diagnosis of otitis media, and when neurologic symptoms appear, they may be due to septic thrombosis of the transverse sinus.

In an irritable infant or child, signs of increased intracranial pressure such as papilledema, ophthalmoplegia, or abnormal pupillary reflexes are difficult for most physicians to assess, yet may be critical in establishing a specific diagnosis and deciding on the type of scan—CT versus MRI—to do to yield the maximal information for the most reasonable cost and safety to the patient. As greater efforts are made to contain the costs of hospital care, consultation by a neurosurgeon or neurologist in such emergency situations may obviate the need for unnecessary studies and direct the evaluation toward the most timely study with the most useful information.

Irritability alternating with lethargy is a common postictal or toxic-metabolic manifestation in children. This may be due to either acute seizure activity or medication side effects, such as phenobarbital or primidone, in a child with a seizure disorder. Determining anticonvulsant drug levels and obtaining an electroencephalogram, a urine toxicology screen, and a consultation may clarify the cause of a child's irritability.

Symptoms such as head tilt, diplopia, or vomiting are associated with tumors of the nervous system, which are the most common form of solid neoplasms of infancy and childhood. Wryneck may also be a sign of atlantoaxial rotary subluxation. Nuchal rigidity without fever may be caused by subarachnoid hemorrhage from a small arteriovenous malformation that has ruptured. If the child is known to have a preexisting neurosurgical disorder, the general practitioner or pediatrician should still proceed with an organized workup and obtain consultation, especially if actual manipulation or tapping of a shunt is indicated. Measuring the child's head circumference and plotting trends on appropriate charts provide useful and complementary information to that obtained from radiographic studies.

By addressing these issues, primary care physicians can then make a reasonable decision as to whether specialty consultation may be warranted for further evaluation and management. There are also several excellent reference sources available.

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Surgical Treatment of Spasticity

In recent years new surgical techniques have been developed that are effective in alleviating spasticity in selected patients. A decade ago, selective dorsal rhizotomy was reported to be effective in alleviating spasticity in children with cerebral palsy; the procedure has since been modified. This neurosurgical operation reduces spasticity by cutting selected posterior nerve rootlets on the basis of intraoperative electrical stimulation and electromyographic recordings. In recent years, interest in this procedure has grown in the United States, and it is being done in several neurosurgical centers across the country. Objective documentation and quantification of the results of this operation as measured by electrophysiologic techniques, physical therapy assessments, and sophisticated gait laboratories are now available.

The procedure is clearly not a panacea for cerebral palsy. It does, however, decrease spasticity, which for some children is a source of major disability. For nonambulatory patients, the operation can increase range of motion; improve sitting, dressing, and positioning; and may lead to gains in functional mobility. For ambulatory patients, it can increase stride length and walking velocity; improve motion about the thighs, knees, and ankles; and ameliorate foot-floor contact. Patients need to be carefully selected with emphasis on ascertaining the clinical importance of obstructive spasticity. Most commonly, cerebral palsy has been the underlying condition, although occasionally patients with spasticity due to myelomeningocele, multiple sclerosis, or head or spinal cord trauma may also benefit.

When chronic pain and spasticity complicate the care of patients with stroke or spinal cord injury, microsurgical lesions at the dorsal root entry zone have been shown to be effective in reducing tone and in alleviating pain.

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Use of High-Dose Glucocorticoids in Acute Head and Spinal Cord Injuries

The efficacy of glucocorticoids in the treatment of acute head and spinal cord injuries has been uncertain. In both instances, experimental work has suggested that these drugs would have a beneficial effect. The results have been mixed, though, when the effect of these drugs has been studied clinically. In patients with acute head injuries, the glucocorticoids appear to reduce mortality but do not improve outcome and do not make the control of intracranial pressure easier. Similarly, with acute spinal cord injuries, no difference in outcome exists between patients treated with standard or those with high-dose methylprednisolone.

The reason that much of the data have been inconclusive has been related to deficiencies in the design of the studies in which the use of glucocorticoids was investigated. These shortcomings in clinical studies have included a reliance on retrospective studies, inadequate controls, unsatisfactory randomization, a failure to blind aspects of studies, a lack of objective evaluation, an insufficient number of patients, and the inclusion of unqualified patients.

Many of these problems in experimental design would seem to have been overcome in the recently completed second National Acute Spinal Cord Injury Study. In this multicenter, randomized, double-blind, and controlled study of 487 patients with acute spinal cord injuries, patients received either methylprednisolone sodium succinate, naloxone hydrochloride, or placebo. Methylprednisolone was administered in the form of a bolus dose of 30 mg per kg given over 15 minutes, followed in 45 minutes by an infusion of 5.4 mg per kg hourly for 23 hours. At six months' follow-up, those patients who had been administered methylprednisolone within eight hours of their injury had a substantial improvement in their neurologic status—motor, superficial pain, and touch sensation—compared with those who had received a placebo. This improvement occurred whether or not patients initially were judged to have either a complete or incomplete spinal cord lesion. The outcome in those patients given naloxone or methylprednisolone more than eight hours after their injury did not differ from that of those who had received a placebo. Major morbidity and mortality were similar in all groups of patients.

The obvious question in light of the demonstrated efficacy of using glucocorticoids in patients with acute spinal cord injuries is whether or not a similar well-designed study is now justified in patients with acute head injuries.

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Warning Leaks and Subarachnoid Hemorrhage

Recent improvements in outcome after a subarachnoid hemorrhage have been attributed to advances in operative and anesthetic techniques, intensive perioperative care, and the recognition and treatment of secondary effects such as hydrocephalus, fluid-electrolyte disorders, and cerebral vasospasm. As perioperative therapy has improved outcome, perhaps the greatest risk to patients with ruptured intracranial aneurysms is inappropriate diagnosis and their delayed referral following a subarachnoid hemorrhage.

The propensity of ruptured aneurysms to rebleed was well documented in the large cooperative studies of the 1970s and 1980s. Recent prospective studies from Scandinavia have substantiated early rebleeding rates from 13% to 22%, with a high percentage occurring within 24 hours of the initial hemorrhage. These studies confirmed earlier observations that the outcome after rebleeding is consider-

ably worse than after a single hemorrhage. Although magnetic resonance imaging is relatively insensitive to acute hemorrhage, aneurysms of greater than 5 mm are frequently visualized and the presence of methemoglobin in the subarachnoid space may be indicative of a previous subarachnoid hemorrhage. In addition, computed tomographic (CT) infusion may localize aneurysms at the circle of Willis with a high degree of sensitivity.

A subset of patients of particular interest are those manifesting a "warning leak." A significant percentage of patients with subarachnoid hemorrhage will describe a transient event of sufficient severity to seek medical attention within three months preceding a major hemorrhage. The prevalence of warning leaks has been estimated at 28% to 59%; patients in this category generally had a worse overall outcome than persons presenting with their initial subarachnoid bleed. Headache was the most common presenting sign of a warning leak in all series, although oculomotor palsy, seizure, nuchal rigidity, transient neurologic impairment, and nausea have been associated with this syndrome. In a study of the characteristics of warning headaches in subarachnoid hemorrhage, most episodes were of sudden onset, localized, occasionally associated with other symptoms, and usually persisted for several days.

Recently 34 patients with warning leaks of less than four weeks preceding a subarachnoid hemorrhage were among a retrospective series of 87 consecutive patients with ruptured intracranial aneurysm. Headache was nearly uniformly present at the time of the warning leak and was unilateral in 52% of patients with aneurysms arising from the internal carotid artery. The diagnosis was missed in all 17 patients who sought immediate attention. Among 9 patients diagnosed before the second hemorrhage, lumbar puncture (100%) was superior to CT scan (45%) in confirming the diagnosis. In 25 patients without diagnosis, a subarachnoid hemorrhage occurred in less than a week for 56% and overall mortality was 53%. Compared with patients presenting with an initial major hemorrhage or diagnosed before rebleeding, those with an undiagnosed warning leak had worse presenting grades, a worse outcome at three months, and a higher incidence of vasospasm and intracerebral hemorrhage.

These data confirm the ominous significance of the warning leak in the natural history of intracranial aneurysms. A recent onset of severe headache or other symptoms potentially referable to a subarachnoid hemorrhage should be promptly evaluated by CT scan. A normal CT scan should be followed by lumbar puncture and a rapid referral for appropriate therapy if indicated. The widespread recognition of the warning leak represents perhaps the greatest area for potential improvement in the treatment of this disorder.

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Radiologic Case

A 38-Year-Old Man With Painful, Dependent Ankle Edema and Clubbing

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A "Radiologic Case" is published in this format on a regular basis. Physicians interested in contributing to the series are encouraged to send their radiologic cases to the series' editor.

JONATHAN M. LEVY, MD
Series' Editor

A 38-year-old man presented with mild edema and arthralgias of his ankles at the end of the day. Both conditions improved with elevation of the feet and the use of anti-inflammatory agents. The patient had smoked a pack of cigarettes per day since age 18. He said he had never had arthritis. Roentgenograms were taken of the ankles (Figure 1).

What is the diagnosis?

What test would you do next?

SEE FOLLOWING PAGE FOR DIAGNOSIS AND DISCUSSION

Figure 1.—Anteroposterior and lateral films of the right ankle show subperiosteal new bone in the distal diaphyseal regions **(arrows)**.

(Grace TW: A 38-year-old man with painful, dependent ankle edema and clubbing. West J Med 1990 Nov; 153:551-552)

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DIAGNOSIS: Hypertrophic Osteoarthropathy Syndrome

Chest films were taken, and the patient was admitted to the hospital a week later for evaluation of a 2-cm coin lesion of the left lung (Figure 2). A bronchoscopic biopsy of the lesion showed adenocarcinoma, and after exclusion of metastases, a left upper lobectomy was done. Clubbing of the digits resolved within three months after the operation (Figure 3).

The hypertrophic osteoarthropathy syndrome is characterized by the presence of periostitis and new bone formation, arthritis, autonomic dysfunction, and clubbing of the digits. This syndrome has also been referred to as hypertrophic pulmonary osteoarthropathy because more than 90% of cases result from disease in the thorax. With the decline of infectious diseases in the antibiotic era, intrathoracic malignant lesions are now the most frequent cause of hypertrophic osteoarthropathy. It occurs in 4% to 12% of patients with primary lung tumors, primarily bronchogenic and pleural carcinomas. It is rare with metastatic tumors of the lung. The syndrome also is seen with cardiac disease (cyanotic congenital heart disease and subacute bacterial endocarditis), liver disease (especially hemochromatosis), gastrointestinal diseases producing acute diarrhea, and various other conditions. The primary form of the syndrome, sometimes called pachydermoperiostosis, may be hereditary or idiopathic. This form is characterized by postpubertal clubbing and bone changes, increased sweating of the palms and soles, and a pronounced thickening of the skin of the face, forehead, and scalp.

Figure 2.—A chest film shows a 2-cm mass in the left lung.

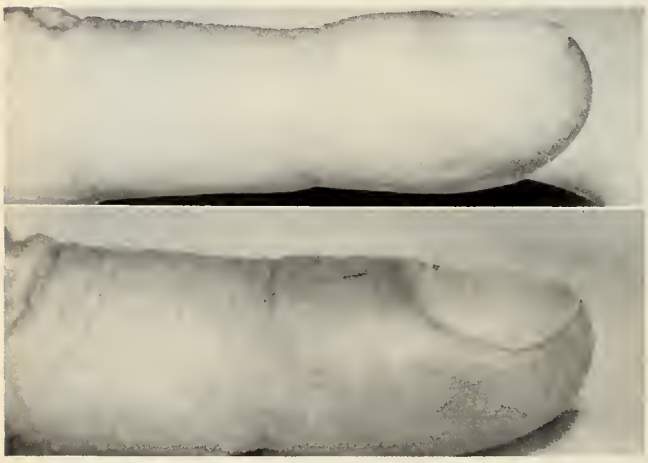

Figure 3.—**Top,** The finger shows preoperative digital clubbing. **Bottom,** There is postoperative regression of the clubbing.

Clubbing of the digits is a prominent feature of the syndrome but is not always present. Because these features can occur independently, different pathogenic mechanisms may exist. Vasodilatation and increased blood flow appear to promote transudation of fluid and fibroblasts into the soft tissues of the terminal tufts, leading to the deposition of collagen. Clubbing can be extremely difficult for patients and physicians alike to recognize, partly because it develops so insidiously. It can precede the clinical appearance of bronchogenic carcinoma by as much as two years, or it can occur much later in the course of the disease. Therefore, this sign is not a reliable indicator for the duration of disease. Clubbing is also neither sensitive nor specific for any particular disease, but its sudden appearance probably heralds a serious disorder.

A unique feature of this syndrome is the aggravation of lower extremity edema and bone pain with dependency. The rheumatic symptoms are rapidly controlled with aspirin or other nonsteroidal anti-inflammatory agents, leading to confusion with the diagnosis of rheumatoid arthritis. The differential diagnosis also includes polyarteritis nodosa, thyroid arthropathy, syphilis, gonococcal arthritis, scurvy, thrombophlebitis, peripheral neuritis, and progressive diaphyseal dysplasia.

When clubbing is associated with periostitis of the distal ends of the long bones, the roentgenogram is the key to the correct diagnosis of hypertrophic osteoarthropathy. The ulna and radius are involved in 80% of cases and the tibia and fibula in 74%. Confirming radiographic findings include a symmetric layering of subperiosteal new bone in the distal diaphyseal regions of long bones. Bone scan changes may precede other radiologic alterations by months, and a "parallel-tract" sign from the pericortical deposition of the tracer in the involved areas should help to distinguish the problem from focal metastatic lesions with their central tracer concentration.

Although the cause of the syndrome is unknown, both humoral and neurogenic factors have been implicated. Surgical resection of a pulmonary neoplasm is not contraindicated by the presence of this disorder. Success in treating the underlying disease process may cause the clubbing or the hypertrophic osteoarthropathy syndrome to regress, as occurred in this patient.

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Alerts, Notices, and Case Reports

Central Nervous System Polyarteritis Nodosa

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POLYARTERITIS NODOSA is the prototypic necrotizing vasculitis capable of affecting multiple systems. Neurologic involvement occurs in 50% to 75% of patients.[1-9] Peripheral neuropathy is the most frequent form of neurologic involvement. The significance of central nervous system involvement is less appreciated. In this report, two illustrative cases of central nervous system polyarteritis nodosa are described, and the English-language literature describing central nervous system manifestations of the disorder is reviewed. The first case has been reported elsewhere in greater detail.[10]

Report of Cases

Patient 1

The patient, a previously healthy 25-year-old man, was admitted to the hospital because of diffuse abdominal pain for four months and a 12-kg weight loss. He complained that worms were crawling out of his nose and boring into his eyes. Family and friends reported no previous abnormal behavior or ideation. He had a history of intravenous amphetamine abuse but said he had not used any drugs in the three months preceding admission.

On physical examination, the patient was in moderate discomfort. His blood pressure was 150/100 mm of mercury, pulse 128 beats per minute, and temperature 38°C (100.4°F). The heart, lungs, and abdomen were normal. A neurologic examination revealed normal sensory and motor function but abnormal mentation as noted. A hemogram was normal except for a leukocyte count of 18.8×10^9 per liter with a normal differential cell count. The admission chemistry panel results were normal except for an albumin level of 21 grams per liter (2.1 grams per dl). A urinalysis showed rare white cells and a trace amount of protein. The results of a spinal fluid examination were normal. A computed tomographic (CT) scan of the head and the findings of a cerebrospinal fluid (CSF) examination were both normal. Tests for hepatitis B and human immunodeficiency virus antibodies were negative. An abdominal CT scan showed a possible right renal cortical infarct.

During his hospital stay, paresthesias of his right leg developed, followed by a right foot drop and a left wrist drop. Abdominal angiography showed multiple mesenteric, hepatic, and renal aneurysms consistent with polyarteritis nodosa. Extravasation from a ruptured renal artery aneurysm was also noted.

The treatment consisted of a regimen of prednisone and cyclophosphamide and gelatin sponge (Gelfoam) embolization of the ruptured aneurysm. His abdominal pain lessened and completely resolved a week later at the time of discharge. Active hallucinations had also stopped by that time. Two days later, he had three generalized tonic-clonic seizures in rapid succession. A second evaluation revealed no other cause for the seizures. Treatment with phenytoin sodium was begun, and no additional seizures occurred.

On a regimen of cyclophosphamide and tapering doses of prednisone, there has been no recurrence of his visual hallucinations and there has been a complete return to normal of his mentation. His wrist drop has resolved and the foot drop has lessened. The phenytoin therapy was discontinued at six months with no recurrence of seizures at one year.

Patient 2

The patient, a 31-year-old woman, was seen because she had had left lower quadrant abdominal pain, left flank pain, and fever up to 39°C (102°F) for a week. Treatment of a presumed urinary tract infection was begun with a combination of trimethoprim and sulfamethoxazole, but her symptoms persisted.

During the next week, the patient had persistent elevations of her diastolic blood pressure to levels between 110 and 120 mm of mercury and a left foot drop developed. A renal angiogram showed bilateral aneurysms, and a diagnosis of polyarteritis nodosa was made. The treatment consisted of methylprednisolone sodium succinate, 1 gram given intravenously, and cyclophosphamide, 125 mg given orally, for three consecutive days. A regimen of prednisone, 60 mg a day, was then started, and the cyclophosphamide was continued. Labetalol hydrochloride and nifedipine therapy was used to control her blood pressure.

Five days later she had four generalized tonic-clonic seizures within a four-hour period. A CT scan of her head and the results of a CSF examination were normal. The findings of a chemistry screen were normal except for a blood urea nitrogen level of 12.1 mmol per liter of urea (34 mg per dl; normal, 3.0 to 6.5 mmol per liter) and a creatinine level of 150 μmol per liter (1.7 mg per dl; normal, 50 to 110 μmol per liter). Her seizures were controlled with phenytoin therapy.

Over the ensuing five months, she has been maintained on a regimen of cyclophosphamide and tapered off prednisone and phenytoin. She has remained seizure-free, her foot drop has diminished, and there has been no further evidence of active vasculitis.

Literature Review

A MEDLINE literature search was done for reports of central nervous system manifestations of polyarteritis nodosa published in the English-language literature between January 1965 and May 1988, postdating the modern classification of vasculitis by Zeek.[11] Articles in which Wegener's granulomatosis was identified or where histologic changes of granulomatous vasculitis were found were excluded when calculating the frequency of specific manifestations.

Clinical Manifestations

The association of polyarteritis nodosa and peripheral neuropathy is well established. Peripheral neuropathy de-

(Rosenberg MR, Parshley M, Gibson S, Wernick R: Central nervous system polyarteritis nodosa. West J Med 1990 Nov; 153:553-556)

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ABBREVIATIONS USED IN TEXT

CNS = central nervous system
CSF = cerebrospinal fluid
CT = computed tomographic
EEG = electroencephalogram

velops in 30% to 70% of patients with the disorder.[1-9] Central nervous system (CNS) manifestations have been less definitively described. Even the frequency of CNS involvement is controversial. Older studies have found CNS involvement to be infrequent. In an autopsy investigation, Rose and Spencer identified evidence of polyarteritis of the brain in only 4% of 54 patients.[12] Arkin cited CNS involvement in only 8% of cases.[13] In a review of patients with polyarteritis nodosa who were observed at the Mayo Clinic, only 4 of 130 patients had CNS manifestations; all were cerebrovascular accidents.[14] In more recent studies, the frequency of CNS involvement has ranged from 15% to 65% of cases of the disorder.[1-3,6-9] Table 1 summarizes the frequency of CNS involvement in published reports appearing after 1975.[1-9]

Polyarteritis nodosa of the central nervous system differs from peripheral neuropathy in its time of presentation. Peripheral neuropathy is frequently the presenting manifestation. In contrast, CNS disease tends to occur two to three years after the diagnosis of polyarteritis.[3,15,16] Central nervous system disease is evident at presentation in 10% to 28% of patients in whom CNS disease will develop.[3,8] All of these patients had other stigmata of polyarteritis nodosa at the time of presentation. We are not aware of any reported cases of this disorder presenting as isolated CNS disease.

Three major forms of CNS polyarteritis nodosa occur: diffuse encephalopathy, focal neurologic deficits, and seizures. These differ in their frequency, pathogenesis, and natural history. They are discussed individually.

Diffuse Encephalopathy

The most frequent form of CNS dysfunction is a diffuse encephalopathy characterized by the loss of intellectual capacity, disorientation, and occasionally psychosis with visual hallucinations. As in patient 1, the onset of the encephalopathy is often insidious. In an early series of polyarteritis nodosa, 23% of patients without clinically evident neurologic disease had abnormalities identified with formal psychological testing.[15] The incidence of clinically diagnosed encephalopathy has ranged from 8% to 20%.[1-4,6]

Complications of the disorder such as hypertension or uremia must be excluded as causes of an altered mental state associated with polyarteritis nodosa. High-dose corticosteroid administration may contribute to the occurrence of psychosis in these patients. Immunosuppressive therapy may increase the frequency of CNS infection. No consistent laboratory abnormalities are found in the patients with encephalopathy. Computed tomographic scans are normal, CSF examinations are unremarkable except for a mild increase in protein content, and an electroencephalogram (EEG) shows only nonspecific slowing. From our review, it appears that the encephalopathic syndrome resolves more readily and more reliably than other CNS manifestations.[3,16] The identification of a vasculitic cause depends on the exclusion of other treatable causes of encephalopathy in a patient with polyarteritis nodosa.

The pathogenesis of the encephalopathy has not been established. The reversibility of the condition and the normal findings on CT scan, CSF analysis, and an EEG suggest a functional, not a structural cause. Older studies describe perivascular inflammation present at autopsy.[17,18] It is postulated that this inflammatory process leads to neuronal ischemia that results in encephalopathy.

Focal Deficits

The second pattern of CNS involvement is that of focal deficits involving the cerebrum, the cerebellum, or the brain stem. In the studies reviewed, the incidence of focal deficits ranged from 3% to 24%.[1-5] In autopsy series, patients with antemortem focal neurologic findings had evidence of cerebral infarction or hemorrhage at necropsy.[17,18] In the only study that consistently recorded CT findings, three of five patients with focal neurologic deficits had infarction or hemorrhage identified on CT.[3] Although some recovery has been seen in these patients, all have residual deficits. Some authors have noted that cerebrovascular accidents tend to occur late in the course of polyarteritis nodosa and often at a time when the vasculitic process is quiescent.[3,5] They theorize that the cerebrovascular events in these patients result from a weakening of the cerebral vasculature subsequent to earlier acute inflammation.[3,5] Cerebrovascular accident was the cause of 23% of deaths in a recent series of 53 patients with polyarteritis nodosa.[5]

TABLE 1.—*Nervous System Involvement of Polyarteritis Nodosa**

Reference	*Patients, No.*	*Peripherol Neuropothy, %*	*CNS Dysfunction, %*	*Encephalopathy, %*	*Focol Deficits, %*	*Seizures, %*
Leavitt and Fauci, 1986[1]†	22	51	23	10	11	4
Duffy et al, 1976[2]	10	30	30	10	10	10
Moore and Fauci, 1981[3]†	25	56	40	20	24	20
Leib et al, 1979[4]‡§	64	72	..	11	3	11
Cohen et al, 1980[5]‖	53	60	..	..	6	4
Scott et al, 1982[6]‡‖	37	62	24	8	..	..
Travers et al, 1979[7]‖	17	59	41	..	..	..
Sack et al, 1975[8]‡‖	40	38	28	..	..	..
Guillevin et al, 1988[9]‡‖	165	68	18	..	..	..

CNS = central nervous system

*All reports that included Wegener's granulomatosis were excluded.
†Patients with more than 1 CNS manifestation were counted in each subtype.
‡Includes patients with lung involvement; excludes other types of vasculitis.
§Unable to identify number of individual patients with CNS polyarteritis nodosa.
‖Insufficient detail to identify number of each subtype of CNS involvement.

Seizures

Seizures, either focal or generalized, occur in 4% to 20% of cases of polyarteritis nodosa.[1-5] The seizures may be multiple.[1-5,19] Electroencephalograms are either normal or show nonspecific slowing.[2,3,15,16] The pathogenesis is unclear but is most likely related to the acute inflammatory process, not chronic structural change, since there are no reports of chronic seizure disorder developing as a sequela of polyarteritis nodosa. Therefore, anticonvulsant therapy should be limited to the period of active vasculitis, rather than continued long term.

Treatment

Most polyarteritis nodosa-induced deaths occur in the initial 6 to 12 months of disease.[4-6] This observation has led to the recommendation for early aggressive therapy. Corticosteroid and cytotoxic agents remain the cornerstones in the treatment of the disorder.[1,20-22]

In two retrospective studies, 28 untreated patients with polyarteritis nodosa had a 13% five-year survival, whereas the five-year survival was 50% for the 144 patients who received prednisone.[4,14] Treatment was at the discretion of individual physicians, and comparison of the two groups is difficult. Sack and co-workers noted increased survival for patients treated with prednisone in doses greater than 40 mg compared with patients given less than 20 mg daily.[8]

Whereas corticosteroids are widely thought to be of benefit,[4,6,8,14,22] controversy exists with regard to the optimal role for cytotoxic agents. While several investigators would reserve the use of cytotoxic agents for patients who do not respond adequately to corticosteroid therapy,[5,9] others consider the alkylating agent cyclophosphamide the drug of choice, particularly for patients with severe disease.[6,21,23] Scott and associates reported on 37 patients with polyarteritis nodosa-type vasculitis.[6] The type of therapy in this study was assigned in a nonrandomized manner by the patients' physician. Of patients receiving no therapy, 50% were alive in six months compared with 67% six-month survival for patients given corticosteroids. Of eight patients treated with combined corticosteroid and cyclophosphamide, six were alive and well 1.5 to 6 years following treatment. In a similar nonrandomized study, Leib and colleagues found five-year survival rates of 12% for supportive care, 53% with corticosteroid therapy, and 80% when an immunosuppressive agent was added to the corticosteroid regimen.[4] It is argued that corticosteroids given alone may produce only a partial remission and may mask smoldering disease activity.[22,23] This may result in progressive damage. In an uncontrolled study at the National Institutes of Health, only three patients died from a group of 17 receiving immunosuppressive therapy (cyclophosphamide for 16 and azathioprine for 1).[23] Two of the three deaths were the result of chronic effects of vasculitis, which was active during therapy with prednisone alone. Leavitt and Fauci consider azathioprine to be less effective than cyclophosphamide in inducing remission but note that it may be useful for maintaining remission.[1]

An assessment of the benefits of therapy for CNS polyarteritis nodosa is complicated by an absence of controlled studies. Also, because CNS involvement usually does not lead directly to death, benefits of therapy must be measured by less definitive end points. At this time, the relative merits of treatment with steroids alone versus steroids combined with cyclophosphamide in CNS involvement can be assessed only on the basis of anecdotal reports. In a report of the clinical course of 25 patients with polyarteritis nodosa, Moore and Fauci describe five patients in whom encephalopathy developed.[3] Encephalopathy developed in four of these patients while they were on steroid therapy. The encephalopathy cleared completely in all five patients when cyclophosphamide was added to their regimen. In the same report, five patients had cerebrovascular accidents while receiving corticosteroids. In contrast, no progression of disease activity was noted once cyclophosphamide was added to the therapeutic regimen. Based on this favorable experience and because of the gravity of neurologic complications as well as the limited healing capacity of the nervous system, these authors recommend limited courses of early aggressive therapy, to include cyclophosphamide, for patients with neurologic polyarteritis nodosa.

The usual oral dose of cyclophosphamide is 2 mg per kg of body weight in conjunction with prednisone, 60 mg daily. The combination is necessary initially because the maximal effect of the cyclophosphamide occurs only after two weeks. The prednisone therapy should be converted to an every-other-day regimen and tapered within the first few months of treatment. Doses of cyclophosphamide should be adjusted so that the leukocyte count remains greater than 3×10^9 per liter and the neutrophil count greater than 1.5×10^9 per liter.[22] After a year of remission, tapering of cyclophosphamide may be attempted.[1]

Only anecdotal information supports the parenteral use of "pulse" steroids or cyclophosphamide or of plasma exchange. Necrotizing vasculitis and acute renal failure were recently reported in a single patient who had reversal of his renal insufficiency by initial treatment with intravenous pulses of both methylprednisolone and cyclophosphamide.[24] There have also been reports on the response and safety of using plasma exchange in the treatment of polyarteritis nodosa.[25-27]

The choice of therapy must be based on considerations of toxicity as well as efficacy. The considerable long-term morbidity of prednisone therapy is well known and will not be detailed.[21,23] Cyclophosphamide therapy may lead to life-threatening infection, acute nonlymphocytic leukemia, and infertility.[28,29] Hemorrhagic cystitis occurs in about 15% of patients.[30] The cumulative risk of bladder cancer in a group of patients with non-Hodgkin's lymphoma treated long term with cyclophosphamide was 10.7% 12 years after the initiation of therapy.[31] The bladder cancer may develop years after the cessation of the cyclophosphamide administration, and long-term surveillance has been recommended.[30,31]

The potential benefits of combined prednisone and cyclophosphamide outweigh the corresponding risks for patients with CNS polyarteritis nodosa. Until further information is available regarding the efficacy of intermittent bolus steroid and cyclophosphamide therapy, we recommend a daily regimen of this combination.

In addition to treating the vasculitic process, clinicians must aggressively detect and manage general medical problems that may occur in these patients. Blood pressures should be followed closely and hypertension treated appropriately. Infections may occur in acutely ill patients as a result of immunosuppressive therapy and the invasive procedures to which they may be subjected.[29] Close surveillance and timely therapy are crucial.

Limitations of Review

It is clear more information needs to be gathered about CNS involvement in patients with polyarteritis nodosa. Articles vary in their method of patient selection.[32-35] The final

diagnosis and listing of clinical manifestations are dependent on physicians' clinical acumen and the degree of diagnostic intervention. Authors may have included patients who would now be classified as having Wegener's granulomatosis, Churg-Strauss vasculitis, or hypersensitivity vasculitis. Case reports may be published because of unusual manifestations and may not accurately reflect the spectrum of the disorder.[36] Thus, certain clinical features may be overestimated. In addition, reports from major academic centers may suffer from referral bias—that is, the most complex of cases are disproportionately represented. Review articles may provide qualitative rather than quantitative information.[16,37] Most critical, no well-controlled randomized studies have evaluated the relative merits of the various therapeutic options.

A prospective series that incorporates modern diagnostic criteria, includes a standardized clinical evaluation, and makes use of newer diagnostic modalities, such as magnetic resonance imaging, would add much to our knowledge of CNS polyarteritis nodosa. Similarly, a prospective randomized therapeutic trial comparing corticosteroid therapy with a regimen of corticosteroids combined with cyclophosphamide would greatly clarify the optimal approach to treating this form of the disease.

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Medicine and Society

Ethics, Jurisprudence, and Economics in the Medical School Curriculum

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Medical ethics, medical jurisprudence, and medical economics are recognized as important components of a medical school curriculum. These subjects were introduced through a course given at the University of California, Davis, School of Medicine. Four aspects of the format and content of the course were instrumental to its success. Teaching principles of medical ethics within the context of jurisprudence and economics permitted the students to gain an understanding of the institutions and processes that act as positive and negative constraints on physicians' clinical and professional behavior. The course was offered during the fourth year following required clinical rotations so that all aspects of the course could be based on the clinical experiences of the students. It was presented in a continuing medical education format away from the normal teaching environment of first- and second-year classrooms and third-year clerkships. Finally, the course was designed by a multidisciplinary, multidepartmental planning group that included students.

(O'Neill LC, Davidson RC, Tupper CJ, Scherger JE, Walsh DA: Ethics, jurisprudence, and economics in the medical school curriculum. West J Med 1990 Nov; 153:557-558)

In 1985 the Liaison Committee on Medical Education of the American Association of Medical Colleges revised the standards of accreditation for medical degree programs in the United States to include the presentation of "ethical, behavioral, and socioeconomic subjects pertinent to medicine."[1] A subsequent survey done in 1987 reported that 95 of 112 responding schools (85%) required a course in human values during the first or second year of the medical curriculum.[1] Debate continues, however, over the most appropriate goals, content, and format for courses in ethical and socioeconomic subjects. We describe a new course at the University of California, Davis, that presents these topics in a successful format.

Teaching Medical Ethics, Jurisprudence, and Economics

The medical school of the University of California, Davis (UCD), has presented topics related to medical ethics and human values as part of the content of preclinical courses since the school opened in 1968. A review of the teaching of medical ethics, medical jurisprudence, and medical economics in the UCD medical curriculum was commissioned by the faculty in 1985 in response to a growing national awareness of the need for increased instruction in these areas. Several preclinical courses included issues in medical ethics. These were presented at different times by separate departments. A survey conducted to ascertain faculty and student perception of how well the subjects of medical ethics, legal issues, and medical economics were covered by these courses revealed a striking disparity between faculty and students. On the issue of medical economics and cost containment, for example, faculty commented that the issue was a "routine part of case discussions," "discussed daily in rounds," or "always considered in rounds and conferences." Third- and fourth-year students, however, reported that the issue of medical economics and cost containment was discussed "nowhere, except [for] an occasional discussion on rounds as to cost of tests." The faculty committee charged with curriculum responsibility concluded that although the students may have received considerably more teaching in the areas of ethics, law, and economics than they perceived, the effect was blunted by the diffuse presentation. This teaching neither fulfilled its presumed purpose nor was it sufficiently comprehensive.

Course Description

As a consequence of these deliberations, a course titled "The Responsibilities of Medical Practice" was introduced as a requirement for all fourth-year students. The goal of the course was to use the topics of medical ethics, medical jurisprudence, medical economics, licensure and physician discipline, substance abuse and physician impairment, and medical quality assurance to address practitioners' responsibilities to patients and to society. The students were encouraged to identify and examine the conflicts presented by the concurrent study of individual and societal needs and values and to identify and examine their responses in the context of clinical decision making, professional conduct, and public health policy.

The format of the course was deemed of critical importance. Exposure to clinical settings was considered a prerequisite, and therefore the course was offered after students had completed the third and half of the fourth year of clinical clerkships. It was thought that mid-fourth-year students anticipating the increased responsibilities of postgraduate training would bring a heightened personal awareness and thoughtfulness to the course. Gathering the entire class together for the first time since their second-year lectures proved to be more beneficial than foreseen. The shared experience of diverse and often intense clinical rotations

From the Office of Curricular Support (Drs O'Neill and Walsh) and the Departments of Family Practice (Drs Davidson, Tupper, and Scherger) and Community Health (Dr Tupper), University of California, Davis, School of Medicine. Dr Tupper is President of the American Medical Association. Dr O'Neill is now a resident in family practice at Santa Rosa Community Hospital, Santa Rosa, California.

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added to the depth with which the issues could be explored.

The course was presented in a two-week block, allowing students to focus on the presentations and the intensity of the discussion without being distracted by clinical duties. Another contribution to the success of the course was the decision to present it in a continuing medical education atmosphere at a local conference center. This format facilitated self- and peer motivation to explore individual and collective values.

The course used didactic lectures, panel discussions, debates, position papers, videotapes, and a mock trial. Most sessions included small group discussions. The faculty planning group gained from the experiences of a course offered by our sister campus at San Francisco.[2] Although attendance was required, self-directed learning and internal motivation were encouraged. Small group discussions were organized and led by students after initial faculty facilitation, allowing the groups to explore issues freely and to develop a sense of autonomy in presenting position statements. Despite initial faculty hesitation, it rapidly became clear that faculty facilitators were not only unnecessary for the discussion groups but actually impeded the productivity of the groups. This continuing education format clearly resulted in the faculty and students becoming "colleagues in learning."[3]

The course was taught by an array of multidisciplinary professionals, headed by the Chair of Record, who was the founding dean of the medical school (C.J.T.). Experts from various professions, organizations, and government institutions were used in presenting topics. For example, "medicine and the law" was presented by members of the Medical and Legal Liaison Committee of the California Medical Association and the State Bar of California and licensure, physician impairment, discipline, and medical quality assurance by the Medical Board of California. The content of the first week of the course was organized around a series of bioethical issues. The selection of such topics as the patient-physician relationship and confidentiality, death and dying and the "right to die," the acquired immunodeficiency syndrome and the right to treatment, and the ethics of reproductive technology and neonatal therapies proved to be an effective means to discuss issues of imminent concern while providing opportunities to explore the broader philosophical basis for ethical decision making. The topics of health care delivery, medical economics, fraud and quackery, and professional conduct were interspersed to provide a perspective of societal issues. The second week of the course concentrated on physicians' personal values and behavior and the regulatory role played by government and professional organizations. The topics medicine and the law, professional liability, physician responsibility and professional review organizations, medical quality assurance, and hospital organizations were introduced to illustrate these relationships.

Evaluation and Discussion

The effectiveness of the course in capturing student interest and imparting an awareness of ethical, legal, and economic issues was evaluated by two methods. A multiple-choice examination was given to students at the beginning and at the end of the course. Students also evaluated the course subjectively by rating each day's presentations and activities for interest, relevance, and quality. Approximately half the class also submitted a more extensive written evaluation of the course. While popularity should not be confused with success, the intensity of participation documented the effect of the course. All respondents evaluating the course recommended that it be continued as a requirement in the curriculum. Students applauded the range of topics presented and the multidisciplinary approach used. A third of the respondents asked for more diversity of topics, including discussions of racism, sexism, and ageism in medicine, current issues in resident training, and an expanded dialogue among attorneys, theologians, patients, and families. The format of presentation was also viewed favorably. Expert panels that encouraged discussion by the class were identified by the students as the most productive method of presenting the material. The class also responded enthusiastically to the debates and the mock trial. Lectures were considered to be the least effective method of presentation by the students.

Conclusion

Medical ethics, medical jurisprudence, and medical economics can be integrated successfully into the education of future physicians. Issues thought by the faculty and students to be critical for the success of such a course include presenting the course as a requirement for graduation, which demonstrates the importance of the subject matter; timing the course in the fourth year of medical school, which allows the students to use their clinical experience as a basis for exploring the issues; developing the course by using a multidisciplinary, multidepartmental planning committee that includes student members; and presenting the course in a continuing medical education format, away from the hospital and clinical rotations and the school's lecture halls, which encourages individual exploration of issues. Although impossible to measure, faculty and students involved thought that such a course will provide a stronger base of understanding of the issues and assist these physicians as they approach practice in the 21st century. As Pellegrino pointed out in his response to the question of whether teaching medical ethics makes a difference,

> There is, for example, no proven correlation between the teaching of anatomy or biochemistry and the scientific quality of a physician's practice. Most of the medical curriculum, it must be admitted, is based on indirect evidence and the faith that exposure to a subject results in some degree of infection.[4]

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Editorials

Good News for Readers

In its pursuit of scientific and clinical excellence, the journal also wishes to be the best written journal available. Therefore, this issue breaks new ground with authors and reviewers (see pages 567 and 568).

Papers must be valid. For that reason, we are increasing biostatistical and epidemiologic reviews of manuscripts, when pertinent.

Because our purpose is to enhance medical care and public health, papers must also be captivating, pithy, and memorable. In order to help make a difference in patient care, authors must not only express clearly their findings and opinions but must keep in mind the readers' wants, needs, and interests. The point is to stimulate and to teach, not simply to publish.

We are joining the ranks of journals trying to simplify and ease readers' lives by printing abstracts that are more structured. The abstracts will be in the same format but organized into purpose, methods, results, and conclusions, presented in that order.

In this era of justified concern regarding conflict of interest, disclosure is crucial. This is true for authors and for peer reviewers. We as editors and you as readers at least must be informed about the possibility of conflicts, then judge results. Thus, authors now have expanded guidelines regarding disclosure of financial interests. Reviewers will be asked to disclose actual or possible personal, professional, and financial conflicts.

Finally, we must join the rest of the world in the use of the Système International (SI) units, but the journal must also be understandable. For now, we have chosen to publish SI units with the familiar metric units following in parentheses. Perhaps by the millennium we will be able to use SI units only.

We hope these changes will be helpful to our readers. Authors will become accustomed to making disclosures and having extensive editorial revisions, and reviewers will become accustomed to considering conflicts they may have before reviewing papers. We hope you will become accustomed to great writing and learning.

LINDA HAWES CLEVER, MD

Diagnostic Tests Should Be Used for Sexually Transmitted Chlamydia

Elsewhere in this issue, Julius Schachter, MD, concisely summarizes recent advances in our understanding of chlamydial infections.[1] Among the most important of these advances has been the development of noncultural diagnostic tests for *Chlamydia trachomatis*. This advance has been long awaited, since chlamydial cultures are available to only a few clinicians and since chlamydial infections often produce minimal or nonspecific symptoms, making their diagnosis and treatment on clinical grounds alone very difficult. Yet, early diagnosis, especially in women, seems critical to prevent ascending upper genital tract infection with its attendant sequelae of pelvic inflammatory disease, peritonitis, perihepatitis, infertility, and ectopic pregnancy.[2] In the absence of an available diagnostic test, it has been recommended that clinicians empirically treat women who present with chlamydia-associated syndromes (such as mucopurulent cervicitis and pelvic inflammatory disease), or who are at high risk because of other infections (gonorrhea) or who have an infected sexual partner. The time has now come to use specific diagnostic tests for sexually transmitted chlamydial infections, just as we do for gonorrhea, syphilis, and other infectious diseases. The anticipated benefits of testing would include establishing a specific diagnosis; enhancing compliance with medications; improving the referral of sexual partners; ensuring a microbiologic cure after therapy; and improving physicians' diagnostic abilities as they gain more experience correlating test results with findings on physical examination.

Testing all women suspected of having mucopurulent cervicitis and pelvic inflammatory disease for chlamydia and then providing empiric therapy until test results are known should become standard practice. Additionally, a strong argument can be made for the periodic screening of women who are at moderate to high risk of chlamydial infection in order to detect asymptomatic infection. These women can be chosen on the basis of risk factors such as young age (especially adolescents), nonwhite race, and new or multiple sexual partners.[3] Studies suggest screening programs using noncultural diagnostic tests are probably cost-effective in populations of sexually active, nonmonogamous young women.[4] Practitioners could easily incorporate such screening into an annual gynecologic examination. The effect of such a program on the prevalence of *C trachomatis* infection has not been rigorously studied, but experience in Seattle where intensive screening has been ongoing in women for several years shows that the prevalence of chlamydial infection has declined, lending support to the effectiveness of this approach. Screening pregnant women seems particularly important in that neonatal infection can be prevented.

A second major point in Schachter's review that is of relevance to clinicians relates to asymptomatic urethritis in men due to *C trachomatis*. Although the disorder has been described for many years, recent studies indicate that in selected high-risk populations (especially adolescents), the prevalence of asymptomatic urethritis may be 5% to 10%.[5] The implication is that such cases are probably an important reservoir for *C trachomatis* infection in the community. Asymptomatic sexually transmitted urethritis due to chlamydia can be strongly suspected in young men whose first-void urine specimen shows pyuria or is positive by the leukocyte esterase dipstick test.[6] These maneuvers may be of particular benefit to clinicians in testing young men who refuse to have urethral swabs inserted into the urethra. The most important benefits to be derived from using first-void urine specimens to test for asymptomatic *C trachomatis* infection in young men, however, will be achieved by the development of screening programs at schools or other relevant locations. The use of a "noninvasive" test (a urine specimen rather than a urethral swab) makes screening far more acceptable to asymptomatic men. Recent studies also suggest that it may well be feasible to make a specific as well as a presumptive diagnosis of chlamydial urethritis by testing the centrifuged urine specimen for chlamydial antigen using an enzyme-linked immunosorbent assay (ELISA) or direct fluorescent antibody technique.[7]

If tests for chlamydia are now to be used, which one should be selected? The plethora of tests now available is indeed confusing. For the most part, commercially available laboratory-based tests for chlamydia can be divided into two types—ELISA assays and direct immunofluorescence slide assays. These tests have been reviewed in detail elsewhere.[7] While each type of test has certain advantages and disadvantages, both when properly done achieve acceptable sensitivity and specificity for clinical use. The test that is best performed by the laboratory a physician uses is probably the test to select. For women, a cervical swab is the specimen of choice, and for men, either a urethral swab or a first-void urine specimen can be used. As reviewed by Schachter, attention to specimen collection is critical. Simplified chlamydial diagnostic tests for use in physicians' offices have recently been marketed. Experience with these tests is evolving, but to date they look considerably less sensitive than laboratory-based tests.

A final area of interest for clinicians in Schachter's review is the rapid growth of knowledge regarding *Chlamydia pneumoniae,* the recently discovered third species of the *Chlamydia* genus.[8] This respiratory pathogen appears to be much like *Mycoplasma pneumoniae:* it spreads within families or other closed populations; produces protracted upper and lower respiratory tract illness, including bronchitis and pneumonia; and can be treated with antibiotics. Unfortunately, the diagnosis is not easy to confirm owing to the organism's fastidious growth in cell culture. Noncultural tests are being developed, however, and a more sensitive cell line has recently been described.[9] Infections may occur in epidemic waves in communities, with a large number of infections in some years and few the next. Thus, knowledge of the current local epidemiology of respiratory infection is important. Practically speaking, serologic diagnosis is the only approach currently available to most clinicians. A single chlamydial complement fixation test that is elevated (titer $\geq$1:64) or a fourfold rise or fall in titer that can be demonstrated during acute and convalescent periods provides support for the diagnosis but is not specific—both *Chlamydia psittaci* and *C trachomatis* also cause elevated antibody levels. Currently, the administration of 2 grams of tetracycline or 200 mg of doxycycline is the recommended therapy.

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Neuroleptics and Tardive Dyskinesia—A Case of Iatrogenesis

NEUROLEPTIC-INDUCED TARDIVE DYSKINESIA (TD) is a unique disorder in that it is the only known potentially irreversible movement disorder caused by a therapeutically administered agent. (Irreversible movement disorders can also be induced by drugs of abuse, such as 1-methyl-4-phenyltetrahydropyridine or MPTP, while reversible dyskinesias are caused by levodopa and several other therapeutic agents.) Another paradoxic characteristic of TD is the ability of the causative agents (neuroleptics) to suppress the pathologic movements. Furthermore, the movements of TD do not necessarily worsen with continued neuroleptic use. These findings highlight the complex pharmacologic and toxicologic nature of TD.

Typically, the age of onset of a number of movement disorders is restricted to one particular stage of life; for example, Gilles de la Tourette's syndrome usually develops in childhood or adolescence and Huntington's disease in early or mid-adult life. By contrast, TD can develop in all age groups, with peripheral choreoathetoid movements being somewhat more common in younger patients and elderly patients having predominantly orofacial movements, at least in the early stages.

The article "Tardive Dyskinesia" by Daniel Casey, MD, elsewhere in this issue[1] provides an excellent overview of this clinically important and unusual iatrogenic disorder. As pointed out by Dr Casey, who is a respected major investigator in the field, TD occurs in approximately 20% of patients on long-term neuroleptic treatment, with a greater prevalence found in high-risk groups, such as the elderly and those with mood disorders. Given the efficacy of neuroleptic agents in ameliorating symptoms in debilitating disorders such as schizophrenia, it is of utmost importance that the potentially irreversible side effects of TD and related tardive syndromes be well understood as to their course, prevention, and treatment.

Chronic schizophrenia is the most frequent indication for the prolonged use of neuroleptic medications, with doses often far exceeding those used in patients with other disorders. Yet, there is some suggestive evidence that these patients may be at a lower risk for the development of TD than patients with mood disorders (especially unipolar depression) and nonpsychotic disorders. This leads to questions about possible factors that might be present in persons with schizophrenia that reduce their vulnerability to the development of TD. Is it possible that the patients who seem to need neuroleptic agents the most—that is, schizophrenics—are relatively resistant to the development of a major adverse effect of those medications? If true, the implications of this possibility are fascinating.

In geriatric practice, neuroleptic drugs are commonly prescribed for treating psychosis and agitation in demented patients. Although they are helpful symptomatically, the improvement produced is usually only modest.[2] Medical patients with intractable nausea and vomiting, severe gastroparesis, and other chronic gastrointestinal difficulties are also frequently treated with neuroleptic medications such as prochlorperazine edisylate (Compazine) and metoclopramide hydrochloride (Reglan). In view of the significant risk of TD, it is imperative that the overall risks and benefits of neuroleptic therapy be carefully weighed in this patient population.

The pathophysiologic mechanism responsible for the development of TD is far from clear. Initially, supersensitivity

of the striatal postsynaptic dopamine receptors was thought to be paramount in the development of TD. Although a number of studies in animals have shown an increase in the striatal D2 dopamine-receptor density after the administration of neuroleptics, this finding has not been correlated with the development of TD. The occurrence of such supersensitivity may therefore be thought of as a normal physiologic response to the administration of neuroleptics, rather than as a phenomenon specifically associated with the pathologic process of TD. Furthermore, the postsynaptic dopamine-receptor supersensitivity measured in animals has been shown to decrease rapidly with the termination of neuroleptic treatment, while TD may abate, remain stable, or even progressively worsen in the weeks to months after the cessation of neuroleptic therapy.

It is unlikely that the pathogenesis of TD involves only one neurotransmitter system. There is evidence for the involvement of the noradrenergic, GABA[γ-aminobutyric acid]ergic, cholinergic, serotonergic, and possibly neuropeptidergic systems in the development of TD. The finding that subgroups of TD patients respond to divergent treatment modalities without there being a single globally effective treatment supports the suggestion that TD represents a group of disorders with differing pathophysiologic mechanisms but similar symptomatic presentations.[3] There is, thus, a need to stop thinking of TD as a unitary disorder resulting from dopamine-receptor supersensitivity and, instead, to view TD as a syndrome with several possible neurotransmitter disturbances.

It is conceivable that the development of persistent TD involves neuronal damage at a structural or ultrastructural level. One proposed mechanism for such cellular damage implicates the production of free radicals from the metabolism of catecholamines in the striatum. Some indirect support for the free radical hypothesis of TD comes from a study by Lohr and co-workers wherein an abatement of TD was shown in some patients treated with α-tocopherol or vitamin E, an effective scavenger of free radicals.[4]

As Casey notes, there is no proven safe and effective treatment for TD, although some patients do respond to pharmacologic manipulations, such as discontinuing anticholinergic agents,[5] adding GABAergic agonists or noradrenergic antagonists, or experimental treatments such as vitamin E. Most often patients should be managed using the "less is better" maxim. This can best be achieved by using the lowest effective doses of neuroleptics rather than "drug holidays" in a majority of patients. There is no evidence that drug holidays decrease the risk of the development of TD. Indeed, many patients with psychotic illness may run the risk, while unmedicated, of having an exacerbation of symptoms with personally and socially deleterious sequelae. It is therefore important to elicit the patient's participation in the decision as to whether the risk for the development of TD with continued neuroleptic use outweighs the risk of symptomatic relapse off medication. If the decision to continue neuroleptics is agreed upon, the patient should be maintained on the lowest effective dose. The discontinuation of treatment should be dependent not on arbitrarily predetermined "holidays," but on a patient's ability to maintain asymptomatic functioning without neuroleptic therapy.

There has been a sharp increase in the number of legal actions initiated by patients with TD over the past several years. These cases have generally been based on claims of negligence in the form of inappropriate assessment, failing to properly manage TD, and failing to obtain informed consent.[6] Although there are widely accepted principles on the necessity to obtain and document informed assent or consent, there is much variation from state to state on the particulars of the law. Furthermore, the relevant laws are evolving within each state. Physicians need to keep abreast of the legislative actions and judicial decisions in the state and county in which they practice.

Although neuroleptics can produce potentially irreversible TD, we must also remember that these potent medications have enabled many patients having chronic psychotic disorders to function better than with most other available treatments. Medical science has yet to develop the ideal medication for psychotic and other severe behavioral disorders: one with all the benefits but without any adverse effects. Therapeutic agents that are site-specific to the dysfunctional areas of the brain are still on the research horizon. Recent studies show some promise toward the development of such specific antipsychotic agents, with low rates of extrapyramidal side effects and TD. An example of this type of antipsychotic is clozapine, the use of which is, however, currently limited to treatment-refractory schizophrenic patients because of the relatively high risk of agranulocytosis.[7] The hope of finding effective and safe therapy for severe mental disorders will best be fulfilled with continued basic and clinical research. Until then, careful and judicious use of the available neuroleptic agents, with the consent of patients, is the best approach.

This work was supported in part by National Institute of Mental Health grants MH-43693 and MH-45131, by California Department of Mental Health grant 90-70067, and by the Department of Veterans Affairs.

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Modern Technology and Unaffordable Costs

THE FISCAL CRUNCHES that now seem to be occurring in this nation at the national, state, and local levels of our society are disturbing. One wonders why everything seems to cost more with less value received for the dollars and resources spent. This is true in both the public and private sectors of society. Is it possible that the resources needed to support modern technology are already in short supply in relation to

an ever-growing need? And if so, could this be an important but unrecognized underlying cause of what are now beginning to be perceived as unaffordable costs? Could it be that modern technology simply costs more than we can afford?

It is possible that health care in this nation may be a bellwether for both the "upsides" and "downsides" of modern technology. Certainly in health care there are examples of the highest development of bioscience and technology and examples of where high cost has placed this modern bioscience and technology beyond the reach of many who could and should benefit from it. It even seems to be beyond the reach of society as a whole to provide what should be available to all, especially those who cannot afford to pay for it for themselves. Somehow, there just do not seem to be enough dollars or enough resources anywhere to make it possible for everyone to reap the full benefits of the health care that modern bioscience and biotechnology have made possible. And the costs of what can be done continue to rise, so far uncontrollably.

The upside of modern technology is obvious enough, and the future seems bright. As far as one can see there will be even greater achievements. This is certainly true in medicine, where bioscience and biotechnology are on a roll. But technologic progress and achievement extend further into the larger society of this nation, where more people are mobile and live and work with advanced technologic assistance, than anywhere else in the world. Other nations aspire to match these technologic achievements, and some seem to have done so. Others have a long way—and some a very long way—to go. But disturbingly, even in this nation there is now some reason to suspect that the overall standard of living is not what it was even a few decades ago. For example, it now takes two workers to support many families when one used to be the norm, and, worse, poverty and homelessness seem to be increasing with each passing year. Could these downsides be related to the increasing dependence of our society on modern technology? One begins to wonder.

It is the conventional wisdom, at least in health care, that costs are too high because of waste, inefficiency, poor judgment, practice errors, greed, overutilization, and even fraud in the delivery system. The high cost of the technology that now is used in virtually every aspect of health care is seldom seen for what it really is. It needs and uses enormous resources of many kinds, and these translate into dollars. For example, the technology and professional skills that come into play in the modern diagnosis and treatment of acute myocardial infarction use many times the resources that were considered appropriate for this condition 50 years ago. And the modern office treatment of diabetes mellitus requires costly technology and uses resources that did not exist 50 years ago. All else notwithstanding, the development and use of modern technology in health care, and elsewhere in the larger society, require and use many more resources that inescapably translate into costs, that is, dollars that have to be paid. This considerable built-in cost has to be a downside of modern technology and the higher standard of health and living that it makes possible.

Are these costs of modern technology actually affordable, in health care or even in the larger society? We like to think they are, but they may not be, simply because resources in demand that are in relatively short supply will always cost more than those that are not. Health care seems to be where this is coming into sharper focus, and it may yet be the crucible from which some of the earliest answers will come. But if one thinks about it, the societal problem is surely much greater than just health care in this nation, or anywhere. Other nations, some very large, aspire to achieve comparable standards of living that will require the development and use of modern technology. They will surely pursue this goal as vigorously as they can. But will there be enough resources for everyone? Or will they always be in relatively short supply and cost more than many can afford? Already, America has begun to feel the fiscal crunches that translate into inadequate resources to meet perceived expectations and even needs. One can readily blame our present national fiscal predicament on poor foresight, waste, mismanagement, greed, or a legalized run on the national purse. This may be true enough. But it may be just as true that modern technology as we now have it in America simply costs more in resources than even this nation can afford. If this is indeed the case, it could be of profound significance in a planetary world now aspiring to match this nation's achievement of a technologic society. At the very least, it does not bode well for any quick fix for the increasing and as yet apparently unaffordable costs of health care.

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The Cost of Nontreatment

To THE EDITOR: The recent shooting in Berkeley, California, that resulted in the deaths of two people and injury to several others follows a tragic yet familiar pattern. Every few months the media thrust upon us the image of people with guns terrorizing their hostages or killing at random and offer shallow explanations such as racism, family problems, or availability of weapons.

The one denominator common to all these cases is the presence of a major psychiatric problem.

Over the past 20 years psychiatric services have been dealt three strikes:

- The government has closed the psychiatric hospitals and has failed to replace them with community facilities as planned.
- The private sector has withdrawn from providing care by severely restricting psychiatric coverage in health insurance and creating barriers to access while downgrading the level of care to counseling.
- The courts have effectively limited the scope of care to those patients who do succeed in entering the psychiatric health care system and have increased the cost dramatically.

Today, at a time when psychiatry can offer more than ever before to the seriously mentally ill, these patients are relegated to the jails or to the streets to suffer alone while the public is denied basic protection.

The price paid by society as a result of the dismantling of the psychiatric health care system is a public health matter and can only be addressed by a major overhaul, including the private sector, the legal constraints, and the public care system.

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Are SI Units Dangerous?

To THE EDITOR: Several leading medical journals, including *WJM, JAMA,* and the *New England Journal of Medicine,* have changed their normal reference values from standard American units to Système International (SI) units. A main argument in favor of this change is that the use of moles is more logical than the use of wholly unrelated units.

There is, however, a strong argument in favor of sticking with conventional units: hundreds of thousands of American physicians and health professionals know and can think in their terms. Under the stress of time pressure, mistakes might be made with a wholesale change. A false sense of accuracy is obtained by their use. For example, an SGOT (now called aspartate aminotransferase) level of 7 to 27 Karman units defines the conditions of the assay.[1] The SI value of 119 to 450 nmol per second^{-1} per liter adds a digit of spurious accuracy and fails to give the conditions of the test.[2] The value will vary depending on the concentration of substrate, the pH, and the temperature of the reaction.

I surveyed about 80 members of the South Bay Pathology Society, representing some 30 hospitals, on this issue of SI units. No hospital was using them, and no pathologist was interested in changing to them. Two members volunteered that the change would "cost me my job." Subsequently, I learned that one of two university hospitals represented is giving consideration to the change, although slowly, and far in the future.

In an attempt to determine if a switch might cause confusion, I devised a pair of clinical questions whose answers would be easy if one knew SI units but impossible otherwise. I hoped to show that the use of SI units was potentially dangerous and to provide evidence that might be used to support a switch of journal style back to conventional units. I asked 18 physicians the following questions:

- Patient 1 complained of chronic diarrhea. She was very thin but not wasted. In attempting to determine the presence of malabsorption, a chemistry panel was done, revealing a cholesterol level of 6.45 mmol per liter. Does this result speak for or against malabsorption?
- Patient 2 was placed on total parenteral nutrition. A serum magnesium value was 1.0 mmol per liter. The next day the value was 1.2 mmol per liter. Are the patient's values high, low, or normal?

The correct answer for patient 1 was "against," as an elevated cholesterol level of 252 mg per dl would rarely occur in a patient with malabsorption. The answer for patient 2 was "normal," as the reference range for magnesium in our hospital is 0.8 to 1.3 mEq per liter when not translated into SI units.

For the first question, 11 physicians picked the wrong answer. For the second, 8 selected the correct answer, while 4 guessed "low," and 6 guessed "high." The results are worse than those obtained from chance alone. Obviously, if the reference range had been given, the answers would have been correct. Some hospital computers, however, cannot print all values with reference "normals." The problem typically arises with remote-site printers and with unsophisticated software systems.

American medicine, like American society, is pluralistic and resists administered change. At a time when physicians have enough problems with outside pressures, we should not make more problems for ourselves.

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EDITOR'S NOTE: *Change is a challenge. We have chosen to meet the SI unit challenge by acknowledging the need to join the rest of the world but not to impair patient care at the same time. Therefore, the journal will print both SI units and standard American units. Perhaps we will learn the Système International units by juxtaposition.*

Ciprofloxacin-induced Anaphylactoid Reactions in Patients Infected With the Human Immunodeficiency Virus

To THE EDITOR: Davis and colleagues have described acute anaphylactoid reactions in 15 patients taking oral ciprofloxacin hydrochloride.[1] Adverse reactions followed the initial dose in 14 patients; 1 patient had taken the drug previously. Six patients required admission to hospital despite

emergency therapy. We report life-threatening anaphylactoid reactions following ciprofloxacin ingestion in two patients infected by the human immunodeficiency virus (HIV).

Patient 1

The patient, a 31-year-old, HIV-seropositive male intravenous drug user with chronic osteomyelitis, was prescribed a regimen of oral ciprofloxacin and metronidazole. A week later the patient stopped both drugs after an erythematous, pruritic rash developed. He subsequently resumed taking both drugs, but a similar eruption occurred. The patient ingested both antibiotics for a third time 4 days later and within 15 minutes had total body erythroderma, pruritus, conjunctival injection, and shortness of breath. In the emergency department, the patient was plethoric and in respiratory distress. He had a blood pressure of 72/40 mm of mercury and a heart rate of 136 beats per minute. Arterial blood gas determinations made while the patient was breathing room air showed a Pao_2 of 55 torr, and a chest radiograph revealed diffuse opacification suggesting pulmonary capillary leak. Volume repletion, diphenhydramine hydrochloride, inhaled metaproterenol sulfate, and subcutaneous epinephrine were given. The patient was given antibiotics and corticosteroids and gradually improved over 48 hours. Cultures of blood and urine were negative for pathogens.

Patient 2

The patient, a 33-year-old, HIV-seropositive woman, was treated with ciprofloxacin for a bacterial urinary tract infection. Five minutes after ingesting the initial dose of the drug, the patient experienced a pruritic rash on her face and trunk, difficulty swallowing, and dyspnea; she subsequently lost consciousness. Cyanosis and stridor were noted by responding paramedics, and the patient was intubated in the field. Her systolic blood pressure was 64 mm of mercury and responded to the administration of saline, epinephrine, and dexamethasone. A chest radiograph showed patchy alveolar infiltrates. Cultures of blood, sputum, and urine were negative for pathogens. Mechanical ventilatory support was given for six days, and the patient recovered without sequelae.

Both of these HIV-infected patients had life-threatening anaphylactoid reactions characterized by erythroderma, hypotension, and respiratory distress. Neither patient was taking any additional medication known to induce anaphylaxis. There were no recognized insect bites or inhalation exposure to chemical toxins. Anaphylactoid reactions to ciprofloxacin in HIV-infected patients have been previously described by Wurtz and co-workers, who reported erythroderma, fever, and hypotension in three patients following ciprofloxacin ingestion.[2] All three patients had received the drug previously. The series by Davis and colleagues provided no data concerning HIV seropositivity.[1] Anaphylactoid reactions to ciprofloxacin have now been reported in 20 patients, 5 of whom were HIV-seropositive. The number of anaphylactoid reactions following ciprofloxacin use suggests that, analogous to the use of trimethoprim and sulfamethoxazole,[3] HIV infection may be associated with an increased incidence of hypersensitivity reactions to this antibacterial agent.

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Lessons From the Practice

An Occupational Hazard

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The power of suggestion is a force to be reckoned with. Although I prepared diligently for all my examinations as a second-year medical student, I found myself totally unprepared for an affliction that was not mentioned in any of my texts: Medical Student's Disease.

This malaise of mindset has plagued young physicians-to-be for centuries. It is characterized by the sudden appearance of symptoms that correspond precisely to whatever illness one is being lectured on at that time. At acute risk is anyone enrolled in pathology or infectious disease courses. The treatments of choice are a weekend spent away from the hospital and library, a trashy novel, or a mindless movie.

During a series of lectures on cardiac pathology, I developed pains in my left chest. Mysteriously, during lectures on pulmonary disease, the pains jumped to the right upper quadrant. Around the time I caught up on the assigned readings on the esophagus, the pains had shifted lower in my chest. Worried that the intensity of my course work was playing with my mind, I kept reminding myself that these aches were mere figments of my inflamed imagination.

I considered dropping by the campus clinic but hesitated to do so. I feared no one would take me seriously given the ambulatory character of my pains and my risk factors for Medical Student's Disease. Moreover, I was a coward. Physicians are notorious for not getting their ailments checked out, and I understood why. I had already heard stories of patients who came into the clinic with trivial complaints, only to be told they had only a few months left to live. I decided to wait and see if everything would clear up on its own.

The pains, however, became more intense. With no one to turn to for help, I applied my recently acquired clinical skills to myself. I auscultated my heart for murmurs and arrhythmias and my lungs for zones of dullness. I palpated lymph nodes and carefully measured my blood pressure. Despite my best efforts, I could make no notable findings.

Then I took a meticulous medical history. What was the character of the pains? Did they coincide with any particular time of day? Were they worse at rest or on exertion? I discovered a strong correlation between the intensity of my discomfort and the number of sodas I drank in a day. Since I knew that heartburn could account for my symptoms quite nicely, I advised myself to find other sources of sugar and caffeine. This treatment worked, and I was relieved to realize my pains were nothing serious.

The next Wednesday, after a poor night's sleep, I arose early to cram for my endocrinology exam. Then, after two more classes, I grabbed my white jacket and black bag and rushed down to University Hospital, where I was to take a medical history and do a physical examination of some unsuspecting patient.

I found my patient, Mr G., in the Cardiac Care Unit, where he had just had a pacemaker installed. At 66 he had a long story to tell: three heart attacks, two episodes of congestive heart failure, an 80-pack-year history of smoking, and a soft spot for fried foods. Mr G. also spent a long time telling me about his heroics as a Navy pilot in World War II. After a protracted physical examination, he began to lecture me about how physicians do not spend enough time with their patients. As I listened to him, I began to feel lightheaded and noticed I was sweating. I excused myself and went into the next room to sit down.

I awoke with an intern and two nurses standing over me. My shirt had been ripped open, and EKG electrodes were pasted across my torso. "Are you all right?" the intern asked me, gazing into my dilated pupils with an intense stare. Before I could answer her, one of the nurses exclaimed, "Look at his EKG. He has ST segment elevations!"

I tried to get up and look at the cardiac monitor, but the nurse immediately pushed me back down. "Oh, my," the other nurse exclaimed, "the EKG computer says he has possible atrial enlargement and valve prolapse!" My God, I thought, the chest pains were real!

A barrage of questions ensued. Did I have any congenital heart defects, murmurs, or arrhythmias? Was I taking any drugs? Had I ever passed out before? When I answered no to everything, she carefully listened to my chest with the bell of her very cold stethoscope.

The intern sent me down to the emergency department. Waiting there, I scrutinized my strips, which had been sent along with me, the whole time feeling my own heart pounding with trepidation. I examined every single wave for abnormalities. I did not see any ST segment elevations. My EKG looked all right to me: rhythm regular, axis decently oriented, magnitudes and width normal. Then again, what did I know? I was only a second-year medical student, and the computer had diagnosed possible atrial enlargement and valve prolapse.

When the emergency physician saw me, he listened to my heart while putting me in a variety of contorted positions. Finally, he asked if I had eaten lunch or had anything to drink. No, I told him, I had been too busy. "Your heart's fine," he said, smiling. "It's a hot day, and you're dehydrated. Go drink a nice cool, tall one."

He told me I had made the mistake of passing out in the wrong place—the Cardiac Care Unit. "The interns up there get cardiac cases referred to them 24 hours a day, seven days a week. The other eight days a week, they read up on rare diseases of the heart. Whatever they see becomes a cardiac

(Lipkin SM: An occupational hazard. West J Med 1990 Nov; 153:565-566)

The author is a third-year medical student at the University of California, San Diego, School of Medicine, La Jolla.
Reprint requests to Steven M. Lipkin, OSA, M-013, UCSD School of Medicine, La Jolla, CA 92093.

problem, at least until another specialist checks the patient out, when the problem then becomes a suspected disease in that specialty."

I realized then that the Medical Student's Disease might not end with graduation. The symptoms I was projecting on myself could later all too easily become projected onto my patients. In a profession approached with such intensity, psychological limits were reached as easily as physical ones. Unless I learned to counterbalance my work with outside interests, the power of suggestion might become an inescapable occupational hazard.

I decided to rehydrate with a weekend off.

THE HOURGLASS

for Edwin M. Kinderman, PhD
Hanford, Washington

You thought
your Peggy would go first,
with her pig's valve
and her strokes, but now

you steer
your own frail wagon
between invisible arrows
and poison darts
that might subdue renegades,
but not before they
(renegades, rays or drugs)
kill you.

You read
statistics to guess your odds,
your ruminating mind
hungry for a new field
in which to browse.

You listen
for genetic messages
whose code was broken
with the wrong cipher book.

You listen
to your body as it cries
its loudest since
your wailing infancy.

You listen
for outlaws escaping cells
to range in other districts
of your traumatized city,
no sirens to pursue them.

You wait
with your nuclear family
for the hot sands of Hanford
to run through the glass.

You wonder
how far *Amanita* spores
have blown on half-life winds
to cloud your horizon,
a fairy ring rippling
from the center of decay.

DAVID OLSEN
Palo Alto, California

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1. Jones JS, Anderson HW Jr, Johnson DW: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978; 292:444-456

2. Berman SM, Shah B, Wyle FA, Dacosta-Iyer M, McRae DM: Disseminated *Pneumocystis carinii* in a patient receiving aerosolized pentamidine prophylaxis. West J Med 1990; 153:82-86

Books

3. Berne EJ: Role playing in therapy, chap 2, Principles of Group Therapy. New York, NY, Oxford University Press, 1966, pp 35-51 (author of book is same as author of chapter)

4. Munsung JD: The role of drugs, chap 2, *In* Brest AN, Mayer JD (Eds): Hypertension—Vol 3, Therapy, 2nd Ed. Chicago, Ill, Year Book Medical Publishers, 1961, pp 456-479 (authors of book differ from chapter author)

Correspondence

5. Shusterman D: Espresso maker's wrist (Correspondence). West J Med 1990; 152:721-722

Government Publications

6. The Health Consequences of Smoking—Cardiovascular Disease: A Report of the Surgeon General. Washington, DC, US Dept of Health and Human Services publication No. (PHS) 84-50204, 1983

7. Centers for Disease Control: Update: Acquired immunodeficiency syndrome—United States. MMWR 1987; 36:522-526

Proceedings

8. O'Connell M: A Controlled Trial of Regional Intra-arterial FUDR Versus Systemic 5FU for the Treatment of Metastatic Colorectal Cancer Confined to the Liver. Presented at the annual meeting of the American Society of Clinical Oncology, San Francisco, December 1989

Mass Circulation Publications (Do not include in reference list; put in text)

(T. Harris, "Selenium-Rich Sediments Also Have Been Reported in Wildlife Refuges," *The Sacramento Bee*, September 8, 1985, p 5)

Personal Communications and Unpublished Data

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Lyme disease has been reported in red squirrels (J. Sneed, PhD, Department of Wildlife, written communication, September 1990).

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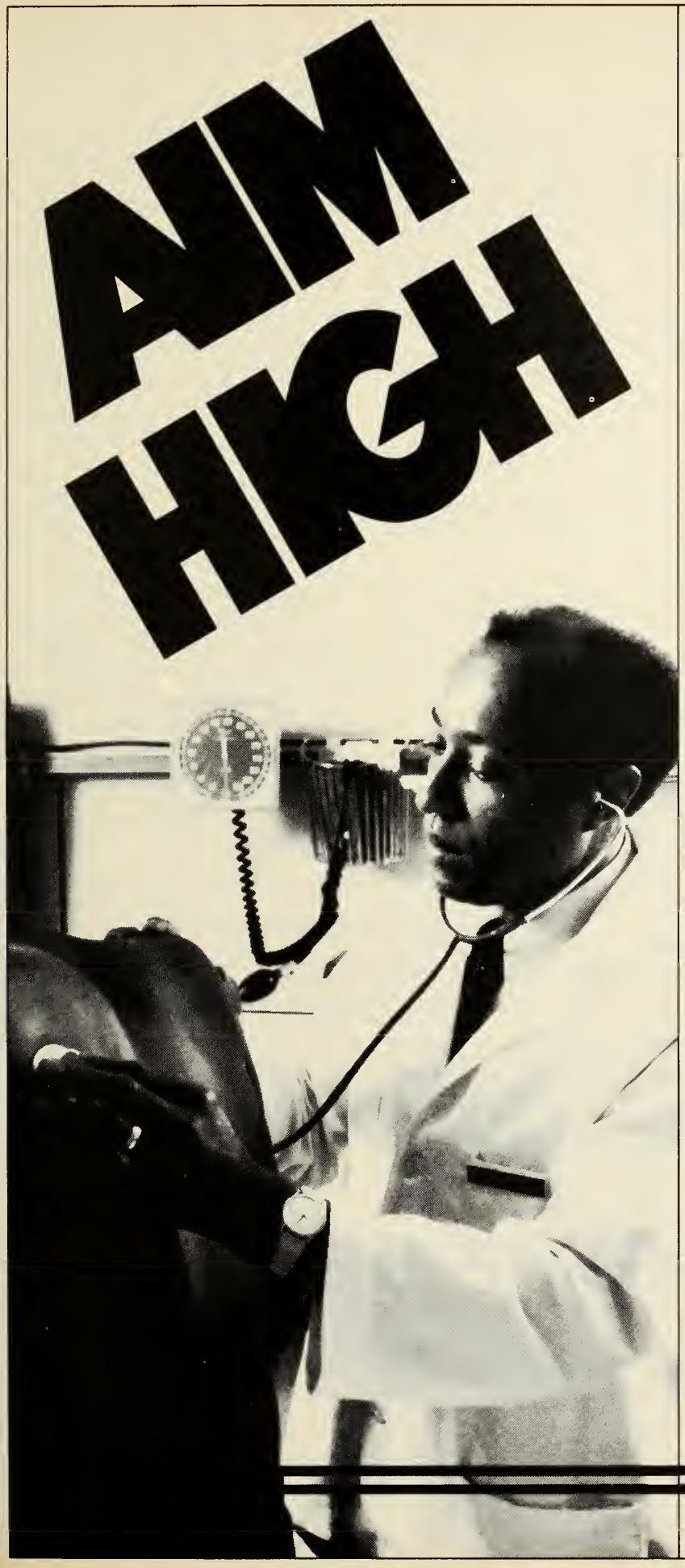

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INTERNIST—PACIFIC NORTHWEST. Excellent opportunity for BC/BE Internist to join group of five Internists in suburban Idaho community. Near urban referral center with good subspecialty backup. Also near superb hunting, fishing, camping, and skiing. Please call or refer résumé to Susan Davis, Administrator, Caldwell Internal Medicine Professional Association, 222 E. Elm, Caldwell, ID 83605; 1 (208) 459-4667.

CALIFORNIA, MONTEREY BAY. Full-/part-time positions available with Monterey Bay's largest and most successful Urgent Care network. Generous guarantee, incentive plan, and benefit package. Malpractice covered. Practice in California's most beautiful coastal recreational area. BC/BE Emergency Room Medicine or Family Practice specialists preferred. Contact Bob Morris, MD, FACEP, Doctors on Duty Medical Clinics, 223 Mt Hermon Rd, Scotts Valley, CA 95066; (408) 438-9341.

PHYSICIANS WANTED

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ReadiCare currently has numerous opportunities in California and Washington state for qualified physicians. We offer:

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Contact:

Marilyn Burke
(800) 237-3234
ReadiCare, Inc
PO Box 2457
Santa Clara, CA 95055

BC/BE PEDIATRICIAN WANTED for semi-rural community 25 miles south of San Francisco to associate with five member Family Practice group. Send inquiry with CV to Lawrence Bruguera, MD, Coastside Medical Clinic, 225 S. Cabrillo Hwy, Ste 100-A, Half Moon Bay, CA 94019; (415) 726-0211.

CALIFORNIA MULTISPECIALTY. Cardiologist, Internal Medicine, Pediatrician, Gastroenterologist, Orthopedist, General/Family Practitioner, Obstetrician/Gynecologist, Dermatologist, General Surgeon. Excellent opportunity for physicians in Los Angeles suburb to join 100 member multispecialty medical group. Large fee-for-service and prepaid practice, no Medi-Cal. Excellent compensation program based on guarantee plus incentive, profit sharing and pension plan. Group provides health, dental, life, and malpractice. Partnership in real estate and medical corporation available. Send CV to Ron McDaniel, Assistant Administrator, Mullikin Medical Center—5, 17821 S. Pioneer Blvd, Artesia, CA 90701.

CENTRAL CALIFORNIA. Join our team of Family Practice Physicians in a progressive community health center near Fresno, California. Competitive salary with extra on-call and overtime. Malpractice paid. Generous vacations and time-off policy. Affiliated with UCSF with on-site Family Practice residents and medical students. Varied practice, including Obstetrics, Pediatrics, and in-patient care with an emphasis on health maintenance, patient education, and primary care research. Position is 60 percent clinical, 40 percent teaching. Bilingual English-Spanish helpful. Contact Ardeth Bier, Fresno County Dept of Health, PO Box 11867, Fresno, CA 93775; (209) 445-3353.

URGENT CARE/PRIMARY CARE PHYSICIANS for over 90 positions available with various physician groups in Phoenix metropolitan/Tucson, Arizona. Excellent compensation and partnership opportunities. Contact Mitch Young, PO Box 1804, Scottsdale, AZ 85252; (602) 990-8080.

PHYSICIANS WANTED

FAMILY PHYSICIANS

Kaiser Permanente, Northwest Region, has excellent opportunities available immediately and in 1991 for BC/BE Family Physicians.

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Portland, OR 97227.
EOE.

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SOUTHERN CALIFORNIA (San Diego County). Thriving coastal city of Encinitas. Three Physician Family Practice Group plus Psychologist seeking residency trained Family Practitioner. Located in new Primary Care/Multispecialty full service facility eight minutes from hospital. Send CV to NCFMG 477 El Camino Real, A306, Encinitas, CA 92024.

OREGON. General Internal Medicine, BC/BE, sought for 10 member, multispecialty group in beautiful rural community, population 16,500, 38 miles southwest of Portland. Send CV to Administrator, 420 E. Fifth St, McMinnville, OR 97128; (503) 472-6161.

GERIATRICIAN/INTERNIST. We are seeking a BC Internist with Geriatric training or certification to join a group of two to practice Geriatric Medicine, actively participate in a university-affiliated teaching program, and assist in program development. Competitive salary and excellent fringe benefits. Send CV to Gary Steinke, MD, Santa Clara Valley Medical Center, 750 S. Bascom Ave, San Jose, CA 95128.

ORTHOPEDIC SURGEON. Immediate opening available for associate Orthopedic Surgeon. Established Orthopedic Practice in North Hollywood, close to St. Joseph Medical Center. For information call office manager Lizzy Regester (818) 506-0999.

SAN FRANCISCO. Primary Care Practice in Noe Valley seeks BC/BE Family Practitioner or Internist to join growing practice. Competitive salary, wonderful neighborhood, partnership option. Send résumé to Noe Valley Family Medicine, 3700 24th St, San Francisco, CA 94114.

FAMILY PRACTICE RESIDENCY FACULTY POSITION—CASPER, WYOMING. University of Wyoming Family Practice Residency-Casper is seeking an experienced, clinically oriented, BC Pediatrician to be the Pediatric Coordinator of an 8-8-8 Family Practice residency program. Level II Nursery skills are a must. 60% teaching, 20% direct patient care, 20% research. This is a tenure track position. University approval will be required prior to filling this position. Come join us in beautiful Wyoming. The University of Wyoming is an affirmative action/EOE. Contact Dr David Driggers, Director, University of Wyoming Family Practice Residency, 1522 E. "A" St, Casper, WY 82601; (307) 266-3076.

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PHYSICIANS WANTED

PHYSICIAN OPPORTUNITIES NATIONWIDE
For all specialities for hospitals, clinics, multi-specialty groups, partnership and solos. Contact Jim Grant in complete confidence at the bay area specialists. **Nugent & Grant, Inc, 1400 Coleman, Ste B-22, Santa Clara, CA 95090; or call (800) 727-2478, FAX # (408) 727-7390.** Never a fee to the physician.

BC/BE NORTHWESTERN CALIFORNIA. OB/GYN needed to join the oldest office in the Redwood area on the north coast. An excellent opportunity for a male or female American trained physician. Excellent compensation and incentive program leading to corporate membership in one year. Three physicians in office but only two doing obstetrics. Send CV and references to T. W. Loring, MD, 2607 Harris St, Ste E, Eureka, CA 95501; (707) 442-4593.

SAN FRANCISCO EAST BAY. BE/BC Internist needed to join ten physician Primary Care group practice in beautiful San Ramon Valley area. Excellent opportunity and compensation. Reply in confidence to Number 223, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

BC/BE FAMILY PRACTITIONER to enjoy rural living with urban culture 20 minutes away. Generous vacation time to use the many nearby recreational opportunities. Join another Family Practitioner and two Physician Assistants in a Family Practice satellite of a large multispecialty clinic. Contact Jerry Corn, MD: (206) 687-5108 or Karen Stanton; (206) 254-1240.

RADIOLOGIST. Major Los Angeles Radiology group is seeking a well-rounded general Radiologist with five to ten years experience to fill unexpected vacancy. Excellent first year salary, early partnership offered. Position involves directorship of an area hospital. Physician must be current and able to perform basic angiography and interventive procedure. Reply to Number 221, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

INVASIVE/NONINVASIVE CARDIOLOGIST. Seeking well qualified noninvasive Cardiologist to join high volume single specialty two member group practice in scenic northern California. Salary guarantee and incentives, with partnership at two years. Send CVs to Number 225, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

EMERGENCY MEDICINE UNIVERSITY POSITION. The University of California, Davis, School of Medicine, is recruiting for a full-time faculty. The position will be at the Assistant or Associate Professor level. The Division of Emergency Medicine and Clinical Toxicology is undergoing rapid academic development and has an approved residency program in Emergency Medicine. The UCDMC Emergency Department provides comprehensive emergency service and is a major trauma center in northern California. The Department is a Paramedic Base Station and Training Center, and in addition, has an active Helicopter Service and Regional Poison Center. Candidates must be BC/BE in Emergency Medicine and be eligible for licensure in California. A letter outlining teaching background, interests, experience, and research in addition to a CV and the names of five references should be sent to Robert W. Derlet, MD, Chair, Emergency Medicine Search Committee, Tr 1219, University of California, Davis, Medical Center, 2315 Stockton Blvd, Sacramento, CA 95817. Applications will not be accepted after December 31, 1990. The University of California is an Affirmative Action/Equal Opportunity Employer.

ORTHOPEDIC SURGEON
BC Orthopedic Surgeon needed for office practice in beautiful southern California area. Full- or part-time, surgery optional. Excellent compensation package. Send CV to **Ronald Gilbert, MD, c/o Gilbert Medical Group, 1076 E. First St, #A, Tustin, CA 92680; or call (714) 832-1516.**

PHYSICIANS WANTED

NORTHERN CALIFORNIA—INTERNAL MEDICINE. The Permanente Medical Group is seeking a BC/BE Internist to join their thriving practice located in Redwood City. Critical care experience helpful but not crucial. We offer a highly competitive salary and a substantial benefits package which includes malpractice insurance, medical, dental and group life insurance, educational leave, an excellent retirement program and a desirable San Francisco bay area location. Please respond with CV to Norman Olson, MD, Chief, Department of Medicine, 1150 Veterans Blvd, Redwood City, CA 94603. EOE.

PRINCIPAL INVESTIGATOR. Physician (MD) to serve as Principal Investigator for clinical research studies involving pharmaceutical products and formulation. These studies include Phase I and dose tolerance projects. This is a part-time position in Phoenix, Arizona, best for a physician with some previous research experience in clinical studies of drug efficacy. Experience in clinical trials preferable but not required. Competitive salary and full benefits package. Send résumé and salary history to Harris Laboratories, Inc, 4638 S. 36th Pl, Phoenix, AZ 85040; (602) 437-0097.

FAMILY PRACTICE OPPORTUNITY. Mission Hills in the San Fernando Valley. Located 20 miles north of Los Angeles. Five physician Family Practice group seeking Family Practitioner to replace retiring physician. Excellent compensation package and partnership potential. Send CV or call Robert Evans, Jackson and Coker, Inc, 115 Perimeter Center Pl, Ste 380 WJMO, Atlanta, GA 30346; 1 (800) 544-1987.

THE VA MEDICAL CENTER AT PRESCOTT, ARIZONA is recruiting for a Board Certified Internist for General Medical, ICU, Respiratory. The Medical Center is a 150-bed general medical and 60-bed nursing home facility with a staff of approximately 650 employees. It is situated on the grounds of historic Fort Whipple. Prescott is a community of 25,000 set in the ponderosa pine foothills of the Bradshaw Range of the Rocky Mountains. At an elevation of 5,400 feet, the climate is temperate with occasional overnight snows in winter and summer highs in the 90s. Outdoor recreation and sports abound—year-round tennis and golf, 100 miles to big mountain skiing, fishing, sailing, boating on beautiful Lake Mead and Lake Powell. Two hundred miles to the excitement and night life of Las Vegas. All this in a quiet tree-lined community with 54 churches, a full service regional medical center, three colleges, six libraries, an excellent school system, a negligible crime rate, no pollution, low taxes, and reasonable housing prices. If you are interested in joining us in this idyllic life style and possess the requisite skill and absolutely spotless professional or employment history, then contact F. C. Lepperd, Jr, MD, Chief of Staff, at (602) 445-4860 ext 301, VAMC, Prescott, AZ 86313. An Equal Opportunity Employer.

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NORTHERN CALIFORNIA

Several positions available for Family Practice, Internal Medicine, and most medical subspecialties. We are a young, aggressive group in a well known prepaid group practice HMO organization with excellent benefits and a very reasonable call schedule. You will have a rewarding practice opportunity with ample time to enjoy the mountains and San Francisco which are nearby. If interested please call or send CV to Physician Recruitment, Administration, The Permanente Medical Group, Inc, 1305 Tommydon St, Stockton, CA 95210; (209) 476-3300.

PHYSICIANS WANTED

SAN FRANCISCO PRIVATE PRACTICE, INTERNAL MEDICINE. BC Internist to join two young, BC General Internists in an estalished fee-for-service practice. Offices are adjacent to one of San Francisco's finest hospitals with an active teaching program. The appropriate candidate must have excellent clinical as well as interpersonal skills to attract patients from competing managed care programs. This is an excellent opportunity to practice first-rate clinical medicine in an independent, exciting environment. (Begin December/January). Send CV to William Andereck, MD, 2100 Webster St, Ste 418, San Francisco, CA 94115.

MULTIPLE FAMILY PRACTICE (BC/BE) positions available in several suburban satellite clinics of a large Seattle area multispecialty group practice. Diverse patient population includes managed care, fee-for-service, and retired military (at some satellite clinics). Competitive salary and excellent benefits. Contact Mary Anderson, Pacific Medical Center, 1200 12th Ave S., Seattle, WA 98144; (206) 326-4111.

RADIOLOGIST—SAN FRANCISCO BAY AREA. Growing outpatient imaging practice with CT/MRI. Salary leading to partnership. Send CV to Murray Solomon, MD, 450 Sutter St, Ste 835, San Francisco, CA 94108; (415) 296-8654.

GENERAL INTERNIST. The VA Medical Center, Long Beach, California is recruiting for a Staff Physician. Duties include seeing patients in Walk-in Clinic, supervision, and teaching of housestaff in clinic. VAMC Long Beach is affiliated with the College of Medicine at University of California, Irvine. Vacancy is full-time position, 40 hours per week. United States citizenship required. Please send CV to David Webb, MD, Associate Chief of Staff, Ambulatory Care (153), VA Medical Center, 5901 E. 7th St, Long Beach, CA 90822; or call (213) 494-5406. Equal Opportunity Employer.

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PHYSICIANS WANTED

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ROCKWOOD CLINIC, PS

An expanding 70 physician multispecialty fee-for-service group seeks BC/BE physicians in the following specialties:

ALLERGY
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CONTACT: **Colleen Mooney, Recruitment Coordinator**
Rockwood Clinic, PS
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Primary Care Physicians and Radiologists needed to work as *locum tenens* statewide. High salary, paid malpractice. Work whenever and wherever you wish. Permanent placements as well. **Western Physicians Registry: Northern California, contact Jim Ellis, Director, (415) 601-7676 or (800) 437-7676. Southern California, contact Tracy Zweig, Director, (805) 643-9346 or (800) 635-3175.**

A BE/BC NEPHROLOGIST is needed to join a two doctor practice in Nephrology forty miles from San Francisco. Excellent modern hospital with Chronic Dialysis unit next door. Superb location in which to live and work. For more information write Thomas I. Paukert, MD, 3443 Villa Lane, Ste 6, Napa, CA 94558; (707) 252-8407.

INTERNIST—SIERRA FOOTHILLS. Excellent opportunity to establish busy practice in growing retirement community. Join dynamic, three BC Internist call group in Grass Valley-Nevada City, with unsurpassed medical facilities, recreational and cultural opportunities. Contact Brad Miller, MD, 970 E. Main St, Grass Valley, CA 95945.

FAMILY PRACTICE PHYSICIAN—CALIFORNIA. Two full-time positions available for physicians in a group practice setting located in central California. Salary very competitive, excellent benefits package and paid malpractice. Additional benefits negotiable including relocation expenses, school loan retirement, possible loan(s) repayment based on longevity. This rural/suburban community location offers easy access to mountain and coastal communities as well as major cities. Please call collect at (415) 226-1421 and ask for Steven R. Grant Placement Director or send CV to MRA—Medical Recruitment Group, 43157 Gallegos Ave, Ste A, Fremont, CA 94539.

FAMILY PRACTICE, SAN DIEGO. Join a seven physician group—all Family Practice, great location. Good pay and benefits. No Obstetrics. Contact Andrea Bower, MD; (619) 745-2000, 815 E. Pennsylvania Ave, Escondido, CA 92025.

SEEKING A PHYSICIAN to associate with a Family Practice group. Ultramodern facility with outpatient surgical suite and industrial medical center. Located in Corona, California, between Orange County and San Diego. Growing area. Good climate. We are offering an association with excellent economic advantage. Contact Ann Holmes at (714) 734-3042.

ASSISTANT/ASSOCIATE PROFESSOR—two positions (non-tenure track), (1) Assistant Medical Director and (2) Obstetrical Coordinator, Las Vegas Family Medicine Center, Department of Family and Community Medicine, University of Nevada School of Medicine. Must be ABFP certified and eligible for licensure in Nevada. Previous practice and/or teaching experience desirable. (1) will be responsible for supervising extended hours in Center and (2) will coordinate obstetrical activities of the department's Las Vegas program. Both positions include teaching medical students, family practice residents, and providing direct patient care. Will be joining new successful program in community based medical school. Send CV to George Hess, MD, Chairman, Department of Family and Community Medicine, University of Nevada School of Medicine, Reno, NV 89557. AA/EOE.

SAN FRANCISCO BAY AREA. Private practice group seeking an associate in Internal Medicine. Family Practice, Pediatrics, OB/GYN opportunities in California and Oregon. For information call/send CV to Bradshaw Associates, 21 Altamount, Orinda, CA 94563; (415) 376-0762, FAX (415) 376-0813.

EUGENE, OREGON. FAMILY PRACTICE. 36 physician multispecialty group is seeking BC/BE Family Physician. OB optional. Excellent schools. Abundant cultural and recreational opportunities. Near Cascade Mountains and coast. Home of University of Oregon. Please send CV to Rob Daugherty, MD, Oregon Medical Group, 2484 River Rd, Eugene, OR 97404; or phone (503) 688-9140.

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Pleasant surroundings conducive to outdoor recreation. Excellent way to unwind from a life of strenuous private practice with rising insurance costs. Staff physician to provide medical care to ICF and psychiatric patients. Research possibilities; 40-hour week flex-time and weekend call. Local university for continuing education. Excellent fringe benefits.

Contact medical director at (505) 454-2422 or

Las Vegas Medical Ctr.
Box 1388
Las Vegas, NM 87701

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PHYSICIANS WANTED

SOUTHERN CALIFORNIA

As one of the nation's oldest and largest managed health care companies, CIGNA Healthplan understands the environment and resources physicians need to practice quality medicine. Currently we have the following opportunities available:

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You will maintain an active clinical practice with a proportion of time dedicated to leadership and management of physician and support staff. Qualifications must include Board Certification in a clinical specialty and prior management experience.

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FAMILY PRACTICE PHYSICIAN. Full-time in a busy walk-in medical clinic. Located in Visalia, California (Tulare County). Malpractice insurance, good salary, etc. Please call (209) 627-5555 for more information.

OB/GYN. Multispecialty group in northwest Washington desires second Obstetrician. Excellent practice opportunity, full range of benefits, early partnership status, all practice costs paid. For more information contact Shane Spray, 1400 E. Kincaid, Mount Vernon, WA 98273; (206) 428-2524.

OB/GYN. BC/BE to join 20 physician (OB, Pediatrics, Internal Medicine) practice in sunny central Washington. Reasonable call schedule with three OB/GYN department. Loan repayment program available. Competitive salary, excellent benefit package including vacation at 30 days per year and professional liability. Contact Ann Garza, Yakima Valley Farm Workers Clinic, PO Box 190, Toppenish, WA 98948; (509) 865-5898.

RHEUMATOLOGY FACULTY POSITION IN CLINICAL RESEARCH. The individual will be one of six Rheumatologists in the Rheumatology Division. The individual will be hired in the clinical track and will be assigned ongoing clinical research projects. It is expected that the individual will design and implement additional clinical studies. The individual should be fully trained in both Internal Medicine and Rheumatology and be eligible for BC in Rheumatology. Academic rank will be based on the individual's experience. Previous experience with clinical trials is preferred but not required. Send CV to Division of Rheumatology, University of Utah Medical Center, 4B218, 50 N. Medical Dr, Salt Lake City, UT 84132.

ACADEMIC INTERNIST. Full-time faculty position for BC Internist at county hospital-based training program in northern California's central valley. Responsibilities include strong emphasis on teaching, administration, and research activities. Send CV or contact Sheela Kapre, MD, San Joaquin General Hospital, PO Box 1020, Stockton, CA 95201; (209) 468-6618. Affirmative Action/Equal Opportunity Employer.

PHYSICIANS WANTED

FAMILY PRACTITIONER GENERAL INTERNIST OTOLARYNGOLOGIST PEDIATRICIAN

Multispecialty group located in San Luis Obispo, California, seeks BC/BE physicians. Fringe benefits plus practice costs paid and shareholder status. Submit your CV to:

Physician Recruitment
San Luis Medical Clinic
1235 Osos St
San Luis Obispo, CA 93401

CENTRAL CALIFORNIA. Anesthesiologist Medical Director needed for high volume teaching hospital. Opportunity to develop contract for services with Kern County. Successful candidate has good track record of leadership with solid clinical background. Please contact Ken Baker, President, Physician Search Group, 120 Montgomery St, Ste 710, San Francisco, CA 94104; (415) 399-8840.

SOUTHERN CALIFORNIA. Established 25 physician multispecialty group offers secure growth opportunity to family oriented OB/GYN and Family Practitioner. Within one hour from the beaches and the mountains. Generous salary, benefits and future ownership. Please contact Ken Baker, President, Physician Search Group, 120 Montgomery St, Ste 710, San Francisco, CA 94104; (415) 399-8840.

OTOLARYNGOLOGIST—DENVER. A successful and well-established ENT practicing in a fast-growing suburb of Denver is now seeking an associate (MD or DO) so he can open a second office. Six-figure first year guaranteed income with future partnership. Send CV to Gordon Crawford, Professional Relations, Humana Inc, Dept HH-11B, 500 W. Main St, Louisville, KY 40201-1438. Or call toll-free 1 (800) 626-1590.

23 PHYSICIAN GROUP PRACTICE. Recent population growth and demand have created the need for several specialists including OB/GYN, Family Practice, Internal Medicine, Cardiology, and Pediatrics in this 23 physician group practice. Situated 60 miles east of San Francisco, the group serves a local population of 35,000. Nearby skiing and boating, reasonable housing, and an excellent school system. Please contact Ken Baker, President, Physician Search Group, 120 Montgomery St, Ste 710, San Francisco, CA 94104; (415) 399-8840.

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General Surgeon
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In Northern Arizona lake country. Guaranteed salary plus bonus; unlimited earning power; ownership potential. Stable, 14-year-old private group practice. Call Marian Parry collect at (602) 645-8823 or FAX CV to (602) 645-2524.

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PHYSICIANS NEEDED

The continuing growth of our service area population (now 90,000) has created an immediate need for additional BC/BE physicians in the following specialities:

- **NEUROLOGY.** Establish private practice with no investment, guaranteed income. Proficiency in EEG, EMG required.
- **GENERAL/THORACIC SURGERY.** Establish private practice in General and Thoracic Surgery (no open heart) with no investment, guaranteed income.
- **ONCOLOGY.** Establish private practice with no investment, guaranteed income. Some General Internal Medicine necessary initially.
- **ORTHOPEDIC SURGERY.** No investment, guaranteed income. Above average earning potential.
- **RADIOLOGY.** Hospital group position. Excellent salary and benefit package. Competency in ultrasound, CAT, Nuclear Medicine, film screen mammography, and general diagnosis required. MRI experience desired. Inpatient and outpatient. (California license is required.)
- **PEDIATRICIAN.** Join busy private Pediatric Practice. Attractive salary with arrangements for future association.
- **FAMILY PHYSICIAN.** Join busy four Family Practice group in private practice. Salary or guarantee first year.

112-bed full service hospital, very well equipped. Excellent ancillary services. Our service area population is now 90,000; a growing area with new businesses and a stable economy.

Located in central California near Sequoia National Park, Tulare offers an excellent family oriented lifestyle and all expected amenities. Beautiful homes, close to hospital and office, are affordably priced. Good schools, many community activities, and abundant recreation including golf, tennis, skiing, mountain and equestrian activities. Easy access to all California's major metropolitan and resort areas.

Contact:
Tulare District Hospital
Physician Recruiting Office
PO Box 90112
Los Angeles, CA 90009
(800) 468-2687

CHEYENNE, WYOMING. Immediate opening available for a dedicated, career oriented, full-time Emergency Physician with Urgent Care facility in Cheyenne, Wyoming. Competitive compensation plus malpractice insurance. Approximately 14 days per month, standard 12 hour shifts. Excellent living conditions, high quality school system, moderate taxes and living expenses, exciting recreational opportunities in the heart of the Rocky Mountain Region. Call now for additional information or send CV to Janet Cowley, Recruitment Coordinator, PO Box 805, Cheyenne, WY 82003; (307) 632-1436, FAX (307) 635-4642.

CARDIOLOGIST—BC/BE sought to join a large hospital based multispecialty clinic. University affiliated residency program. Excellent fringe benefits. Competitive salary. California license required. Send CV to Aung-Win Chiong, MD, The Permanente Medical Group, Inc, 2025 Morse Ave, Sacramento, CA 95825.

SANTA CLARA, CALIFORNIA. The Permanente Medical Group of Santa Clara, Sunnyvale, and Milpitas has career positions available for BC/BE General Internists. We are a multispecialty group with a 337-bed Stanford affiliated teaching hospital. We have our own freestanding Internal Medicine Residency Program with opportunities for teaching and research. Competitive salary and excellent benefits package. Send CV to Sheryl Sun, MD, Kaiser-Permanente Medical Group, 900 Kiely Blvd, Santa Clara, CA 95051.

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PHYSICIANS WANTED

INTERNISTS. Las Vegas and Reno, Nevada; Dallas and Victoria, Texas; New Orleans suburbs and Shreveport, Louisiana; West Palm Beach and Hollywood, Florida. Private practices with established physicians. For details, call Eloise Gusman, 1 (800) 535-7698 or send CV to PO Box 1685, Covington, LA 70434-1685.

GENERAL SURGEON, LAS VEGAS, NEVADA. Group of five surgeons are seeking a replacement surgeon. For details, call Eloise Gusman, 1 (800) 535-7698 or send CV to PO Box 1685, Covington, LA 70434-1685.

NORTHERN CALIFORNIA—SAN FRANCISCO BAY AREA. Leading HMO is seeking BC/BE physician to staff a busy, urban, full-service Emergency Department with the possibility of administrative advancement. Kaiser Permanente is a large pre-paid HMO offering competitive salary, job security, shareholder status and generous benefits including health care, life insurance, disability insurance, sick leave, mortgage assistance, and educational leave. Please address all inquiries to David Witt, MD, Emergency Department, Kaiser Permanente Medical Center, 1200 El Camino Real, AD-WJM, South San Francisco, CA 94080-3299; or call (415) 742-2516. EOE.

TWO INTERNISTS seek an associate BE/BC Internist for busy Internal Medicine group practice located in a community of 60,000. Forty miles from San Francisco. Excellent modern hospital. Superb location in which to live and work. For more information write Thomas I. Paukert, MD, 3443 Villa Lane, Ste 6, Napa, CA 94558; (707) 252-8407.

UNIVERSITY OF CALIFORNIA, DAVIS MEDICAL CENTER. The University of California, Davis, Department of Emergency Medicine is searching for physicians residency trained or BC in Emergency Medicine. The Health Science Campus is located in Sacramento and serves a large area of northern California. The Emergency Department cares for over 60,000 patients a year. The Center operates as a Level One Trauma Center, has paramedic base station training responsibilities, and has a helicopter service. An approved Emergency Medicine Residency Program began in July 1990. Emergency Physicians supervise medical students, interns, and residents, in addition to having direct patient responsibilities. Support for clinical research is available to those interested. University compensation is competitive, and fringe benefits include health and dental insurance, three weeks paid vacation, one week continuing medical education, social security, UC retirement plan, 12 paid holidays per year, and full malpractice coverage. Send CV to Robert W. Derlet, MD, Chief, Division of Emergency Medicine, University of California, Davis, Medical Center, 2315 Stockton Blvd, Sacramento, CA 95817.

SAN FRANCISCO BAY AREA BC/BE INTERNISTS

We are currently seeking highly qualified Internists and subspecialists to complement our energetic Internal Medicine team. Department members provide a full range of medical services for a population of over 200,000 pre-paid health plan members. Recently renovated and expanded medical center facilities are within convenient commuting distance to virtually any bay area city, and the extensive cultural and recreational activities of northern California. As part of our large, multispecialty group practice, you would enjoy an excellent salary, generous fringe benefits, a flexible schedule, and the opportunity for academic affiliation with prestigious local institutions. Send CV to:

Winslow Wong, MD
Attn: Administration
Kaiser Permanente Medical Center
27400 Hesperian Blvd
Hayward, CA 94545

EOE

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THE BEST OF BOTH WORLDS

Join our rapidly expanding and well established multi-specialty group practice in Southern California. It's the ideal environment for physicians who are seeking a small community atmosphere, combined with the latest medical resources and technology of a major force in the health care industry.

Immediate practice opportunities available for Physicians in the following specialties:

- ***Family Practice***
- ***Internal Medicine***
- ***Obstetrics/Gynecology***
- ***Pediatrics***
- ***Orthopedic Surgery***
- ***Otolaryngology***

We offer an excellent compensation and benefits package including ***professional liability coverage, life and disability insurance, medical/dental coverage, paid vacation, sick leave and paid educational time.***

For more information, send your CV to Box #217, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

NEUROLOGY RESIDENCY. PGY-2 position available July 1, 1991, University of Utah Medical Center. Candidates must have PGY-1 training in Internal Medicine in United States or Canadian accredited program and be eligible for licensure in United States. Contact Dr John E. Greenlee; (801) 584-1218 at VA Medical Center, 500 N. Foothill Dr, Salt Lake City, UT 84148, or Dr Richard Baringer; (801) 581-4283. The University of Utah is an Equal Opportunity Employer.

MULTISPECIALTY CLINIC in the Phoenix suburban area is seeking a BC/BE Pulmonologist with an interest in Critical Care to join our 26 physician, fee-for-service clinic. Excellent professional and financial opportunity. Send CV to Executive Director, Arizona Medical Clinic, Ltd, 13640 North Plaza del Rio Blvd, Peoria, AZ 85381.

OCCUPATIONAL MEDICINE, SAN FRANCISCO BAY AREA. Area's leading multispecialty private group practice is seeking BC/BE physician to join their expanding Department of Occupational Medicine. Range of practice includes pre-employment physicals, diagnostic evaluations, treatment of on-the-job injuries; comprehensive knowledge of all areas of Occupational Medicine. Competitive salary, plus incentive, excellent benefits, paid malpractice. Located in the South Bay which offers wonderful cultural/recreational activities, fine dining, outstanding climate and scenery, easy access to beach and mountains. For further information, please send CV or contact Maureen Forrester, San Jose Medical Group, Inc, 45 S. 17th St, San Jose, CA 95112.

OPPORTUNITY for full- and part-time Emergency Physicians. Excellent fee-per-patient load ratio. Malpractice paid. Also, Emergency Department/Family Practice positions for urgent care/industrial center. Send CV to Front Line Community Physicians, PO Box 10610, Santa Ana, CA 92711, or contact Medical Director at (714) 771-3290.

PHYSICIANS WANTED

TUCSON, ARIZONA FAMILY PRACTICE

An immediate need exists to join this busy Family Practice adjacent to Northwest Hospital in the newly completed medical office building. Call and coverage is one to five. A generous salary, plus bonus and expenses, is provided. Should you require additional information, please call:

Herbert Jalowsky, MD
(602) 742-0414

or forward your CV to:

1925 W. Orange Grove Rd
#105
Tucson, AZ 85701

SOUTHERN CALIFORNIA. 300-bed hospital in growth community at foothills of Mt Baldy. Opportunity for OB/GYN, Family Practice, and Rheumatologist to associate with successful practitioners. Hospital will provide generous guarantee, moving expenses, and practice management assistance. Please contact Ken Baker, Physician Search Group, 120 Montgomery St, Ste 710, San Francisco, CA 94104; (415) 399-8840.

CALIFORNIA MEDICAL/LEGAL DISABILITY EVALUATIONS. Opportunities available in Sacramento, San Jose, Salinas, Oakland, and San Diego for BC physicians in Dermatology, Internal Medicine, Orthopedics, Ophthalmology, Otolaryngology, Psychiatry, Toxicology, and Neurology with a multispecialty medical group which provides forensic medical evaluations. This is an excellent opportunity to supplement income as well as associate with a well respected medical group whose practice is limited to evaluations. Send inquiry and CV to Terence Doyle, Disability Reporters, 696 E. Santa Clara St, Ste 105, San Jose, CA 95112; (408) 283-8689.

CENTRAL CALIFORNIA. Hospital based teaching opportunity for OB/GYN in a new residency program at the KMC. Ideal candidate is a team player with a strong desire to teach residents. This UCLA affiliate has a busy OB department with 5,000 deliveries per year. Please contact Mary Letterii, Vice President, Physician Search Group, 120 Montgomery St, Ste 710, San Francisco, CA 94104; (415) 399-8840.

RADIOLOGIST FOR SOUTHEASTERN UTAH. Excellent practice opportunity to join second Radiologist. Primary service area of 30,000 people with 88-bed community hospital. Nuclear, CT, mammography, ultrasound, and radiography. Contact Milton Bauermeister, MD, Castleview Hospital, Price, UT 84501; (801) 637-4800, ext 280 or (801) 472-5403.

(Continued on Page 578)

(Continued from Page 577)

PHYSICIANS WANTED

FAMILY PRACTICE WESTERN WASHINGTON

Highly compatible 12 member group (seven Family Practitioners/four Internal Medicine/one Surgeon) seeking 8C/8E Family Practitioner with interest in 08. Quality medical care our highest priority. Facilities divided into sections of four to five MDs to give "small clinic" feel with "large clinic" sophisticated x-ray, lab, endoscopy, treadmill, in-house consultation, professional management. Seaport town, headquarters to Olympic National Park. Rainfall 24 inches per year, outstanding air quality, unparalleled recreation, excellent schools and cultural opportunities without big city traffic. Contact **Bill Kintner, MD, Port Angeles Clinic, 433 E. 8th St, Port Angeles, WA 98362; (206) 452-3373.**

SOLANO COUNTY HEALTH SERVICES DEPARTMENT currently has an opening for Clinic Physician-MCH Director and full-/part-time Clinic Physicians. No on-call, no graveyard hours, no hospital responsibility. 45 minutes to either San Francisco or Sacramento. Please send CV to Solano County Human Resources Dept, 580 Texas St, Fairfield, CA 94533; (707) 421-6170. EOE/AA.

WE SEEK PRIMARY CARE PHYSICIANS for challenging opportunities, competitive salaries and flexible schedules. Register by sending CV or call in confidence: Annashae Corporation, 6593 Wilson Mills Rd, Cleveland, OH 44143-3404; 1 (800) 245-2662.

FULL-TIME TRAVEL REQUIRED (one year minimum). Health research organization needs physicians for National Health and Nutrition Examination Survey sponsored by the US Public Health Service. Individuals will be part of a large medical team conducting health examinations in government examination centers traveling to 68 areas of the US through 1993. Physicians must be licensed in one state. Competitive salary, paid malpractice, per diem, car, four weeks paid vacation per year, holidays, and health, life, dental, disability insurance offered. Call Beverly Geline at (800) 937-8281, ext 8248. Westat, Inc, Rockville, MD. EOE/M/F/V/H.

INTERNIST—SAN FRANCISCO BAY AREA. An Internist practicing in an East Bay community of 75,000 for the past 37 years is now seeking another Internist to take over his practice. This practice numbers between 400-500, many of whom have been patients for 20 plus years. Send your CV to Gordon Crawford, Professional Relations, Humana Inc, Dept HH-11A, 500 W. Main St, Louisville, KY 40201-1438. Or call toll-free 1 (800) 626-1590.

PULMONOLOGIST. Coastal north San Diego County. Join solo Pulmonologist. Must be willing to do 50% Internal Medicine. Proficiency with ICU and procedures necessary. Can accommodate less than full-time arrangement. Apply 2067 W. Vista Way, Ste 265, Vista, CA 92083.

OBSTETRICS/PEDIATRICS. Small multispecialty group seeks second Pediatrician and OB/GYN to work with present physicians. Excellent compensation and benefits. Looking for long-term partnership. Call or send CV to Craig Kaner, Administrator, All Care Medical Group, 2675 E. Slauson Ave, Huntington Park, CA 90255; (213) 589-6681.

INTERNAL MEDICINE. Full-time BC/BE Internist for multispecialty group in southeast Los Angeles. Office/hospital and consulting practice. Spanish a plus. Top salary, benefits, and malpractice insurance. Potential for partnership second year. Send CV to Craig Kaner, Administrator, All Care Medical Group, 2675 E. Slauson Ave, Huntington Park, CA 90255; (213) 589-6681.

FAMILY PRACTITIONER. Full-time, BC/BE for growing multispecialty medical group in southeast Los Angeles. Some Spanish helpful. Top salary, benefits, and malpractice. Partnership potential second year. Send CV or call Craig Kaner, Administrator, All Care Medical Group, 2675 E. Slauson Ave, Huntington Park, CA 90255; (213) 589-6681.

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Billing and Corporate Support Provided

For additional information on opportunities and locations contact

Glenn W. Farmer
Director

Catherine M. Dawson
Assistant Director

1-800-527-2145

EGSI, 1717 Main Street, Suite 5200
Dallas, Texas 75201
214/761-9200

MEDICAL CLINICAL RESEARCHER to coordinate research and development of articular cartilage repair devices and further development of isobone substitute. Identify and develop biological and synthetic based implantable devices. Work with medical profession. PhD in Medical Clinical Research. No work experience required but two years training in articular cartilage repair. $865 per week. Job and interview in Tustin, California. Send copy of advertisement and résumé to Job Number DC-18919, PO Box 9560, Sacramento, CA 95823-0560 no later than December 15, 1990.

ARIZONA. Thomas-Davis Medical Centers, PC, a rapidly expanding multispecialty group practice of 110 plus physicians in Tucson, Green Valley, and Phoenix, Arizona has positions available in these cities in Family Practice, Internal Medicine, and Pediatrics. Excellent fringe benefits and profit sharing program. Guarantee for first two years, plus incentive. Early shareholder. Fee-for-service, as well as physician owned HMO. Must be BC/BE. Call or write Bill De Long (602) 322-2525 or James J. Vitali, CEO, (602) 322-2525 at Thomas-Davis Medical Centers, PC, PO Box 12650, Tucson, AZ 85732.

SACRAMENTO, URGENT CARE. $120,000 guaranteed at free standing, hospital affiliated clinic with an annual census of 18,000. Prestigious northern California group seeks qualified, experienced physicians, BC or BP in specialty. Additional opportunities at two area hospitals' ED Fast Tracks. Paid malpractice and generous profit sharing. Contact Art Wong, MD, FACEP, Emergency Physicians' Medical Group, 120 Montgomery, Ste 1000, San Francisco, CA 94104; (415) 989-1242.

OPPORTUNITY FOR GENERAL SURGEON with Thoracic and Vascular experience. Salary leading to partnership. Northern California surgical group in northern California rural community. Excellent quality of life. 1165 S. Dora, A3, Ukiah, CA 95482; (707) 462-7579.

HEMATOLOGIST
ONCOLOGIST
CARDIOLOGIST
ENDOCRINOLOGIST
NEUROLOGIST

Multispecialty group practice located in the Puget Sound area. Please send CV with reply to:

Number 212
Western Journal of Medicine
PO Box 7602
San Francisco, CA 94120-7602

PHYSICIANS WANTED

SOUTHERN CALIFORNIA

Upscale, family oriented community in the eastern foothills of Los Angeles County offers qualified primary care physicians (Family Practice, General Internist, Pediatricians) both group and private practice opportunities. Complete compensation package includes salary guarantees, practice management and marketing support, malpractice, and relocation expense reimbursement. BC/BE. Excellent growth potential. Send CV to Gary May, Foothill Presbyterian Hospital, 250 S. Grand Ave, Glendora, CA 91740; or call (818) 963-8411.

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CLASSIFIED ADVERTISING INFORMATION
(415) 882-3376

(Continued on Page 580)

The Permanente Medical Group, Inc.
Northern California

Quality

The Permanente Medical Group, Inc., the largest multispecialty group practice in the U.S., is undergoing explosive growth in its Northern California region: the San Francisco Bay Area, Sacramento and the Central Valley. Our rapid increase in membership has created practice opportunities throughout the region.

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Our physician-managed group is part of the comprehensive Kaiser Permanente Medical Care Program. As a TPMG physician, you have access to the latest medical technology and resources, the support of colleagues in all subspecialties — and the opportunity to provide excellent health care without the burdens of managing a practice.

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Growth

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Join us in one of these facilities:

- Walnut Creek/Pleasanton/Danville
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- Oakland
- South Sacramento/Stockton
- Santa Rosa
- San Jose/Gilroy
- San Francisco
- South San Francisco
- Sacramento/Roseville/Davis/ Rancho Cordova
- Richmond
- Redwood City
- Fresno
- Hayward/Fremont
- Santa Clara/Milpitas/Sunnyvale
- Vallejo/Fairfield/Napa
- San Rafael/Petaluma/Novato

TPMG offers many benefits: scheduled time off with cross-coverage provided by your colleagues, continuing education, malpractice insurance, a substantial retirement program and special arrangements for physicians transferring from established practice. For complete information, call or send CV to: The Permanente Medical Group, Inc., Richmond Prescott, M.D., Physician Recruitment Services, Dept. WJM-9240, 1814 Franklin, 4th Floor, Oakland, CA 94612. (800) 777-4912. Equal Opportunity Employer.

KAISER PERMANENTE
Good People. Good Medicine.

(Continued from Page 578)

PRACTICES AVAILABLE

FOR SALE. Established, busy Urology practice in southwestern New Mexico. No investment required. Excellent year 'round climate and outdoor recreational opportunities. Call collect, Pierson Deming, MD, (505) 388-1561 (office) or (505) 388-4557 (home): or call Steve Jacobson, Administrator, Gila Regional Medical Center, (505) 388-1591.

FAMILY PRACTICE FOR SALE. Established 30 years solo Family Practice fully equipped and furnished. Well rounded practice, block from hospital, teaching hospital six miles away. Excellent location, growing area 65 miles north of San Francisco in Wine Country. Share call five weekdays and one weekend per month. Available to stay to introduce new physician. Financing available. Please contact Richard C. Barnett, MD, 9323 Lakewood Dr, Windsor, CA 95492; or call (707) 838-3383.

ESTABLISHED FAMILY PRACTICE for sale in Cody, Wyoming. Purchase price of $180,000 includes a 1,735 square foot building designed for dual practice. Owner financing available. Call Brokerage West, (307) 587-6234.

COLORADO COLLEGE TOWN. General Internal Medicine and Geriatric practice and building for sale. $250,000, variable terms. Solo corporation. Great place to live. Call 1 (303) 482-4510 evenings.

PRACTICE FOR SALE in beautiful southwest Montana. Boating, fishing, camping, hunting, and skiing at your doorstep. Family Practice with terminations of pregnancy. Price: $50,000, negotiable. Reply to Number 224, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

SALT LAKE CITY, UTAH. Internal Medicine Practice—Office Condominium—for sale, 1,400 square feet. Space for Pharmacy or second professional. Suitable for clinic or Family Practice. On public transportation. Parking. Excellent living. Call (801) 355-3822.

PEDIATRIC PRACTICE FOR SALE. Retiring Board Certified Pediatrician plans to sell his practice and rent his office adjacent to a first rate hospital in the bay area of California. Night and weekend calls are shared with four independent Board Certified Pediatricians. This practice is within the Stanford Medical Community. Send CV to Joseph Donovan, 433 Palmer Ave, Aptos, CA 95003; (408) 688-4954.

NORTHERN CALIFORNIA. Urgent and Routine Care Clinic. Currently limited as a one physician operation. Large patient base. 2,600 square feet. Fully equipped and computerized. Collecting $265K. Country setting. Reply to Number 205, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

SAN DIEGO COUNTY. Family, Internal, OB/GYN and Pediatric practices available. Long established—doctors retiring. Various prices and low down payments. Call CBI, San Diego County's professional practice sales specialists, (619) 283-7009.

HAYWARD. Fully equipped office for sale or rent to Internist or Pulmonologist. Practice based on therapy which has consistently relieved asthma and COPD for the past 30 years. Contact J. J. Robbins, MD, 1634 B St, Hayward, CA 94541; or (415) 581-3451.

NORTHERN AND CENTRAL CALIFORNIA. Established practices available: Dermatology, Family, Internal Medicine, GYN, Personal Injury, Plastic Surgery. Reasonable terms and prices. Call/write Bradshaw Associates, 21 Altamount, Orinda, CA 94563; (415) 376-0762, FAX (415) 376-0813.

SAN DIEGO NORTH COUNTY. Ambulatory Care Family Practice/Occupational Medical Center. Gross $530,000. Well located, attractive, fully equipped 2,700 square foot office. Open 7 days per week. Contact Practice Consultants, Dr Bernard Press, Broker, (619) 528-2321.

DON'T FORGET!

The deadline for submitting classifieds for the January issue of WJM is November 26.
Send your advertisement to:

Classified Advertising WJM, PO Box 7602 San Francisco, CA 94120-7602

(415) 882-3376

EXCEPTIONAL OPPORTUNITY

This family practice and home is now for sale. The approximately 8,000 sq ft facility includes a modern clinic with three examination rooms, a minor surgery room, x-ray, laboratory and medical records areas.

This property borders The Redwood National Park and features a two story home on ten acres of land with panoramic views of the Pacific Ocean and just two and a half miles from growing downtown area.

Please call 907-464-4393 for information or write to:
Point St. George Medical Clinic,
Crescent City, CA 95934

PRACTICES AVAILABLE

NORTHERN CALIFORNIA. Family Practice established 1978. Gross 350K plus. Must sell for health reasons. Well equipped, good shared call schedule. No OB, no medical, minimal night call. Asking $78,000. May purchase over time or may lease. Reply to Number 227, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

PUGET SOUND AREA (south of Tacoma). Purchase active Family Practice with over $325,000 gross. No OB. 1/5 weekend call coverage. Shared office with one Family Practitioner. Fully equipped with x-ray and laboratory. Number 226, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

PLACEMENT SERVICES

NURSE PRACTITIONERS, PHYSICIAN ASSISTANTS, NURSE MIDWIVES. We provide the right mid-level professional for your clinical setting. Western Practitioner Resources, Heidi Bourne, RN, Director. (800) 345-5859 or (707) 839-5859.

COURSES

SKI—CME EUROPE or HELI-B.C. $25.00. Rainier Educational Emprize. T. Akamatsu, MD, 502 N. Stadium Way, Tacoma, WA 98403; (206) 572-4619.

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GENERAL SURGEON, BC, experienced. Desires relocation to California, Washington, or Oregon. Prefers group, clinic, or HMO. Consider solo with coverage. Experienced in continuing medical education, quality assurance, utilization review. Reply to Number 228, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

ATTENTION ADVERTISERS

WJM Classified Advertising has a new phone number:

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You may now dial us directly.

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(Continued from Page 580)

CONFERENCES

WORKSHOP ON FALLOPIAN TUBE CATHETERIZATION

Oregon Health Sciences University
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January 19-20, 1991

- Offers hands-on didactic instruction in new transcervical methods for fallopian tube catheterization
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- Lectures address a variety of clinical applications and are supplemented by small group discussion
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- Tuition Fee: $400 (hospital group rate available)

- **Course Directors:** Miles J. Novy, MD and Amy Thurmond, MD
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For further information contact:
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Oregon Health Sciences Univ
Portland, OR 97201-3098
(503) 494-4898

NINTH ANNUAL MEDICAL SEMINAR at Plummer's Great Slave Lake Lodge, Northwest Territories, Canada. July 20-27, 1991. Topics in contemporary medicine. All specialties. Approved 23 CME credits, category 1. Sponsored by North Memorial Medical Center and University of Minnesota Department of Family Practice and St. John's Regional Health Center, Springfield, Missouri. Contact (612) 588-9478.

Fifth Annual Central Oregon Oncology Conference on:

THE BRAIN AND CANCER: SCIENCE AND PSYCHOLOGY

January 31-February 2, 1991

Inn of the Seventh Mountain, Bend, Oregon

Co-sponsored by St. Charles Medical Center, Bend, Oregon; The Oregon Health Sciences University, Portland Oregon; The American Cancer Society, The Oregon Division

For further information, contact:
Lois Gibson, St. Charles Medical Center
2500 NE Neff Rd, Bend, OR 97701
(503) 382-4321

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WANTED: CLINICAL LABORATORIES. We are interested in considering the purchase of clinical laboratories—either independent or group practice. For further information, please write Winchester Management Ltd, PO Box 22007, Nashville, TN 37202.

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MEDICAL OFFICE SUITE, 1,246 square feet, in Santa Maria Medical-Dental Arts Building. Under construction. Tenant occupancy to begin in July. Tenant improvement to suit tenant. Adjacent to surgi-center with covered doctor parking. Terms of lease to be negotiated. Call (818) 994-5454.

GROWTH AREA OF SANTA CLARA VALLEY. New medical office space for lease in the growth area of Silicon Valley, Morgan Hill, California. Easy access, abundant parking, well located, generous tenant improvement allowances. Excellent patient referral sources. Contact Dr Jon Hatakeyama, (408) 779-7391.

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ORTHOPEDIC, OB/GYN AND INTERNAL MEDICINE PHYSICIANS. 1,400 square foot new medical office available in beautiful Willamette Falls Health Center in a rapidly growing area near Portland, Oregon. Reserve parking, conference room, immediate access to freeway. Current tenants include Family Practice, Internal Medicine, Dermatology, Immediate Care and Oral Surgery. Contact Christy Carl at (503) 654-7111.

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General Medical clinics and Acupuncture College. Staff runs college, knowledge of acupuncture not required. 150 students, student loans, immigration approved. Established 10 years, 500k gross, real estate option available. PO Box 591033, San Francisco, CA 94158; (415) 383-9371 8 am-noon.

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The Western Journal of Medicine

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SPECIAL ISSUES

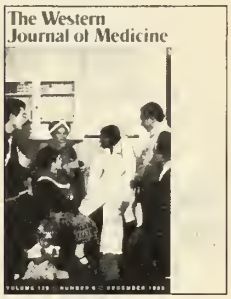
Addiction Medicine
and the Primary Care Physician

Addiction Medicine and the Primary Care Physician was conceived to be part of the initiative to expand the involvement of all specialties of medicine in the prevention and treatment of addictive disease. Topics covered include chemical dependence and the workplace, alcoholism, methadone maintenance in the treatment of opioid dependence, nicotine dependence, and treatment of cocaine dependence. David Smith MD, Special Editor, 1990.

Women and Medicine

This special issue explores both the professional side of women in medicine and the diagnosis and treatment of women patients. Topics covered include liver disease, women and AIDS, heart disease, hysterectomy, PMS, ovarian cancer, and women physicians and organized medicine. Linda Hawes Clever, MD, Special Issue Editor, 1988.

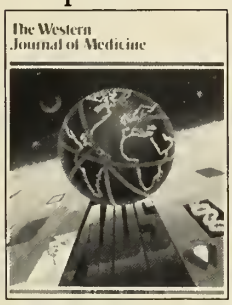
Cross-cultural Medicine



Cross-cultural medicine is devoted to the care of patients of different cultural, ethnic, or religious backgrounds. Subjects include Southeast Asian refugees in the American health care system, psychiatry and Chinese culture, health and illness in Filipino immigrants, and health care of Middle Eastern patients. M. Margaret Clark, PhD, Special Issue Editor, 1983. 2nd reprinted edition.

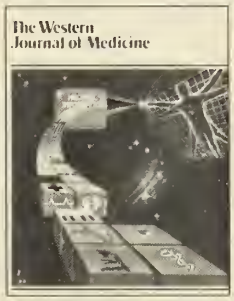
Also available:

AIDS—A Global Perspective



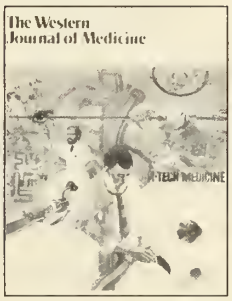
Jonathan M. Mann, MD
Special Issue Editor, 1987

Medical Informatics



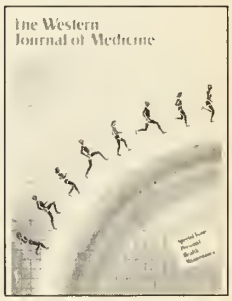
Marsden S. Blois, MD
Special Issue Editor, 1986

High-Tech Medicine



R. Paul Robertson, MD
Special Issue Editor, 1985

Personal Health Maintenance



John H. Holbrook, MD
Special Issue Editor, 1984

Please send me:

_____ copies of Addiction Medicine and the Primary Care Physician

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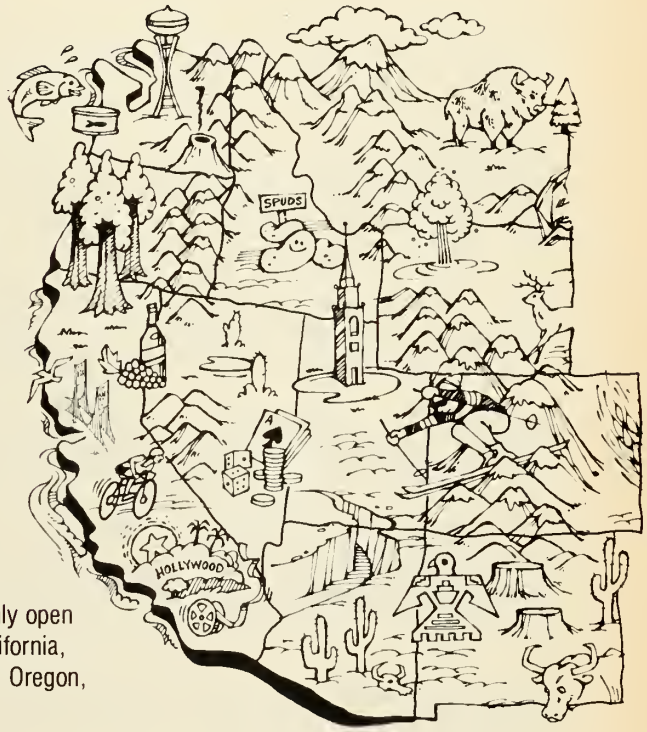

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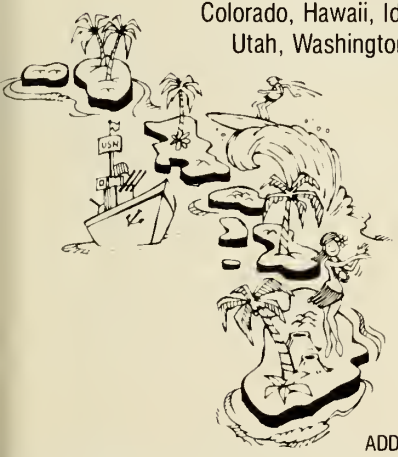

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Alaska State Medical Association—2401 E 42nd Ave, Suite 104, Anchorage 99508. (907) 562-2662. Annual Meeting: 1991, date and location to be announced.

Arizona Medical Association, Inc—810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: 1991, date and location to be announced.

California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 8-13, 1991, Bally's Grand Hotel, Reno.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: 1991, date and location to be announced.

Hawaii Medical Association—1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: 1991, date and location to be announced.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: 1991, date and location to be announced.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: 1991, date and location to be announced.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 25-28, 1991, Quail Lodge, Carmel, California.

New Mexico Medical Society—7770 Jefferson, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: 1991, date and location to be announced.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting (House of Delegates only): 1991, date and location to be announced.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: 1991, date and location to be announced.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: 1991, date and location to be announced.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: 1991, date and location to be announced.

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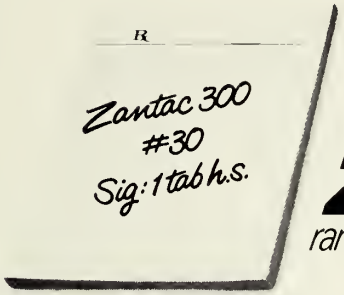
In active duodenal ulcers

Once-a-night hs therapy controls acid rain



Zantac® 300
ranitidine HCl/Glaxo 300 mg tablets

Zantac® 150 Tablets
(ranitidine hydrochloride)

Zantac® 300 Tablets
(ranitidine hydrochloride)

Zantac® Syrup
(ranitidine hydrochloride)

BRIEF SUMMARY

The following is a brief summary only. Before prescribing, see complete prescribing information in Zantac® product labeling.

INDICATIONS AND USAGE: Zantac® is indicated in:
1. Short-term treatment of **active duodenal ulcer**. Most patients heal within four weeks.
2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathological hypersecretory conditions** (eg, Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of **active, benign gastric ulcer.** Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated.
5. Treatment of **gastroesophageal reflux disease (GERD).** Symptomatic relief commonly occurs within one or two weeks after starting therapy. Therapy for longer than six weeks has not been studied.

In active duodenal ulcer; active, benign gastric ulcer; hypersecretory states; and GERD, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: Zantac® is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS:

General: 1. Symptomatic response to Zantac® therapy does not preclude the presence of gastric malignancy.
2. Since Zantac is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since Zantac is metabolized in the liver.

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during Zantac therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although Zantac has been reported to bind weakly to cytochrome P-450 *in vitro*, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions that suggest that Zantac may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2,000 mg/kg/d.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, Escherichia coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Zantac. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Zantac is secreted in human milk. Caution should be exercised when Zantac is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with Zantac®. The relationship to Zantac therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to Zantac administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported.

Cardiovascular: As with other H_2-blockers, rare reports of arrhythmias such as tachycardia, bradycardia, atrioventricular block, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, abdominal discomfort/pain, and rare reports of pancreatitis.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid intravenously for seven days, and in 4 of 24 subjects receiving 50 mg qid intravenously for five days. There have been occasional reports of hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice. In such circumstances, ranitidine should be immediately discontinued. These events are usually reversible, but in exceedingly rare circumstances death has occurred.

Zantac® 150 and 300 (ranitidine hydrochloride) Tablets
Zantac® (ranitidine hydrochloride) Syrup

Musculoskeletal: Rare reports of arthralgias.

Hematologic: Blood count changes (leukopenia, granulocytopenia, thrombocytopenia) have occurred in a few patients. These were usually reversible. Rare cases of agranulocytosis, pancytopenia, sometimes with marrow hypoplasia, and aplastic anemia have been reported.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by Zantac and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when Zantac has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving Zantac, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia), anaphylaxis, angioneurotic edema, and small increases in serum creatinine.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: (See complete prescribing information in Zantac® product labeling).

Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice daily. An alternate dosage of 300 mg or 20 ml (4 teaspoonfuls equivalent to 300 mg of ranitidine) once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.

Maintenance Therapy: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day. In some patients it may be necessary to administer Zantac® 150-mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/d have been employed in patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day.

GERD: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day.

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with Zantac, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: **Zantac® 300 Tablets** (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 (NDC 0173-0393-40) tablets and unit dose packs of 100 (NDC 0173-0393-47) tablets.

Zantac® 150 Tablets (ranitidine hydrochloride equivalent to 150 mg of ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 60 (NDC 0173-0344-42) and 100 (NDC 0173-0344-09) tablets and unit dose packs of 100 (NDC 0173-0344-47) tablets.

Store between 15° and 30° C (59° and 86° F) in a dry place. Protect from light. Replace cap securely after each opening.

Zantac® Syrup, a clear, peppermint-flavored liquid, contains 16.8 mg of ranitidine hydrochloride equivalent to 15 mg of ranitidine per 1 ml in bottles of 16 fluid ounces (one pint) (NDC 0173-0383-54).

Store between 4° and 25° C (39° and 77° F). Dispense in tight, light-resistant containers as defined in the USP/NF.

July 1990

Glaxo Pharmaceuticals
DIVISION OF GLAXO INC.
Research Triangle Park, NC 27709

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Now Medi-Cal Approved

CONTROL ACID RAIN

with once-a-night hs therapy for active duodenal ulcers

Zantac® 300

ranitidine HCl/Glaxo 300 mg tablets

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See adjacent page for Brief Summary of Product Information

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Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology

Increasing the risk of
Peripheral Arterial Disease

Diabetes stacks the odds against microcirculatory flow

In diabetes, atherosclerotic changes occur above *and* below the knee, often involving smaller vessels and multisegmental occlusions.[1] Diabetes has also been *associated* with decreased red cell flexibility, and increasing fibrinogen levels, platelet aggregation and platelet adherence, factors which predispose patients to peripheral arterial disease.[1]

Duration of Diabetes	Incidence of PAD
10 years	15%
20 years	45%

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Now Medi-Cal approved
for patients with diabetes who have been diagnosed as having intermittent claudication
Drug Type Code: 5041AHE

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Trental® improves microcirculatory flow and lifestyle for many diabetics with PAD

Trental® (pentoxifylline) increases red cell flexibility[2] while decreasing elevated plasma fibrinogen levels,[3] aggregation of platelets[4] and red cells.[5] The resulting increase in microcirculatory flow enhances tissue perfusion and oxygenation.[6]

With Trental, patients experience significant improvement in pain-free walking distance, paresthesia, skin temperature and subjective overall response.[7]

Not a vasodilator • Not an anticoagulant • Not related to aspirin or dipyridamole

Trental® 400 mg Tablets (pentoxifylline)

The only proven-effective agent for intermittent claudication, a symptom of peripheral arterial disease

Please see references and brief summary of prescribing information on following page.

Trental® can improve function and symptoms, but is not intended to replace more definitive therapy, such as surgery.

References:
1. Levin ME, Sicard GA: Evaluating and treating diabetic peripheral vascular disease, Part I. *Clinical Diabetes* May/Jun 1987. **2.** Stormer B, Kleinschmidt K, Loose D, et al: Rheological changes in the blood of patients with chronic arterial occlusive disease after the administration of vasoactive drugs. *Curr Med Res Opin* 1977;4:588-595. **3.** Perego MA, Sergio G, Artale F: Haemorrheological aspects of the pathophysiology and clinical features of peripheral occlusive arterial disease. *Pharmatherapeutica* 1983;3(1):91. **4.** Seiffge D: *IRCS Med Sci* 1980;8:727. **5.** Lowe GDO, Drummond MM, Forbes CD, et al: Blood and plasma viscosity in prediction of venous thrombosis. Abstracts: 77, International Symposium on Filterability and Red Blood Cell Deformability, Göteborg, Sweden, Sep 11-13, 1980. **6.** Ehrly AM: Effects of orally administered pentoxifylline on muscular oxygen pressure in patients with intermittent claudication. *IRCS Med Sci* 1982;10:401. **7.** Schubotz R: Double-blind trial of pentoxifylline in diabetes with peripheral vascular disorders. *Pharmatherapeutica* 1976;1(3):172-179.

Trental® (pentoxifylline) Tablets, 400 mg

A brief summary of the Prescribing Information follows.

INDICATIONS AND USAGE:
Trental® (pentoxifylline) is indicated for the treatment of patients with intermittent claudication on the basis of chronic occlusive arterial disease of the limbs. Trental® (pentoxifylline) can improve function and symptoms but is not intended to replace more definitive therapy, such as surgical bypass, or removal of arterial obstructions when treating peripheral vascular disease.

CONTRAINDICATIONS:
Trental® (pentoxifylline) should not be used in patients who have previously exhibited intolerance to this product or methylxanthines such as caffeine, theophylline, and theobromine.

PRECAUTIONS:
General: Patients with chronic occlusive arterial disease of the limbs frequently show other manifestations of arteriosclerotic disease. Trental® (pentoxifylline) has been used safely for treatment of peripheral arterial disease in patients with concurrent coronary artery and cerebrovascular diseases, but there have been occasional reports of angina, hypotension, and arrhythmia. Controlled trials do not show that Trental® (pentoxifylline) causes such adverse effects more often than placebo, but, as it is a methylxanthine derivative, it is possible some individuals will experience such responses.
Drug Interactions: Although a causal relationship has not been established, there have been reports of bleeding and/or prolonged prothrombin time in patients treated with Trental® (pentoxifylline) with and without anticoagulants or platelet aggregation inhibitors. Patients on warfarin should have more frequent monitoring of prothrombin times, while patients with other risk factors complicated by hemorrhage (e.g., recent surgery, peptic ulceration) should have periodic examinations for bleeding including hematocrit and/or hemoglobin. Trental® (pentoxifylline) has been used concurrently with antihypertensive drugs, beta blockers, digitalis, diuretics, antidiabetic agents, and antiarrhythmics, without observed problems. Small decreases in blood pressure have been observed in some patients treated with Trental® (pentoxifylline); periodic systemic blood pressure monitoring is recommended for patients receiving concomitant antihypertensive therapy. If indicated, dosage of the antihypertensive agents should be reduced.
Carcinogenesis, Mutagenesis and Impairment of Fertility: Long-term studies of the carcinogenic potential of pentoxifylline were conducted in mice and rats by dietary administration of the drug at doses up to approximately 24 times (570 mg/kg) the maximum recommended human daily dose (MRHD) of 24 mg/kg for 18 months in mice and 18 months in rats with an additional 6 months without drug exposure in the latter. No carcinogenic potential for pentoxifylline was noted in the mouse study. In the rat study, there was a statistically significant increase in benign mammary fibroadenomas in females in the high dose group (24 × MRHD). The relevance of this finding to human use is uncertain since this was only a marginal statistically significant increase for a tumor that is common in aged rats. Pentoxifylline was devoid of mutagenic activity in various strains of *Salmonella* (Ames test) when tested in the presence and absence of metabolic activation.
Pregnancy: Category C. Teratogenic studies have been performed in rats and rabbits at oral doses up to about 25 and 10 times the maximum recommended human daily dose (MRHD) of 24 mg/kg, respectively. No evidence of fetal malformation was observed. Increased resorption was seen in rats at 25 times MRHD. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Trental® (pentoxifylline) should be used during pregnancy only if clearly needed.
Nursing Mothers: Pentoxifylline and its metabolites are excreted in human milk. Because of the potential for tumorigenicity shown for pentoxifylline in rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.
Pediatric Use: Safety and effectiveness in children below the age of 18 years have not been established.

ADVERSE REACTIONS:
Clinical trials were conducted using either controlled-release Trental® (pentoxifylline) tablets for up to 60 weeks or immediate-release Trental® (pentoxifylline) capsules for up to 24 weeks. Dosage ranges in the tablet studies were 400 mg bid to tid and in the capsule studies, 200-400 mg tid.
The table summarizes the incidence (in percent) of adverse reactions considered drug related, as well as the numbers of patients who received controlled-release Trental® (pentoxifylline) tablets, immediate-release Trental® (pentoxifylline) capsules, or the corresponding placebos. The incidence of adverse reactions was higher in the capsule studies (where dose related increases were seen in digestive and nervous system side effects) than in the tablet studies. Studies with the capsule include domestic experience, whereas studies with the controlled-release tablets were conducted outside the U.S. The table indicates that in the tablet studies few patients discontinued because of adverse effects.

INCIDENCE (%) OF SIDE EFFECTS

	Controlled-Release Tablets		Immediate-Release Capsules	
	Commercially Available		Used only for Controlled Clinical Trials	
	Trental®	Placebo	Trental®	Placebo
(Numbers of Patients at Risk)	(321)	(128)	(177)	(138)
Discontinued for Side Effect	3.1	0	9.6	7.2
CARDIOVASCULAR SYSTEM				
Angina/Chest Pain	0.3	—	1.1	2.2
Arrhythmia/Palpitation	—	—	1.7	0.7
Flushing	—	—	2.3	0.7
DIGESTIVE SYSTEM				
Abdominal Discomfort	—	—	4.0	1.4
Belching/Flatus/Bloating	0.6	—	9.0	3.6
Diarrhea	—	—	3.4	2.9
Dyspepsia	2.8	4.7	9.6	2.9
Nausea	2.2	0.8	28.8	8.7
Vomiting	1.2	—	4.5	0.7
NERVOUS SYSTEM				
Agitation/Nervousness	—	—	1.7	0.7
Dizziness	1.9	3.1	11.9	4.3
Drowsiness	—	—	1.1	5.8
Headache	1.2	1.6	6.2	5.8
Insomnia	—	—	2.3	2.2
Tremor	0.3	0.8	—	—
Blurred Vision	—	—	2.3	1.4

Trental® (pentoxifylline) has been marketed in Europe and elsewhere since 1972. In addition to the above symptoms, the following have been reported spontaneously since marketing or occurred in other clinical trials with an incidence of less than 1%; the causal relationship was uncertain:
Cardiovascular—dyspnea, edema, hypotension.
Digestive—anorexia, cholecystitis, constipation, dry mouth/thirst.
Nervous—anxiety, confusion.
Respiratory—epistaxis, flu-like symptoms, laryngitis, nasal congestion.
Skin and Appendages—brittle fingernails, pruritus, rash, urticaria, angioedema.
Special Senses—blurred vision, conjunctivitis, earache, scotoma.
Miscellaneous—bad taste, excessive salivation, leukopenia, malaise, sore throat/swollen neck glands, weight change.
A few rare events have been reported spontaneously worldwide since marketing in 1972. Although they occurred under circumstances in which a causal relationship with pentoxifylline could not be established, they are listed to serve as information for physicians: Cardiovascular—angina, arrhythmia, tachycardia; Digestive—hepatitis, jaundice, increased liver enzymes; and Hemic and Lymphatic—decreased serum fibrinogen, pancytopenia, aplastic anemia, purpura, thrombocytopenia.

OVERDOSAGE:
Overdosage with Trental® (pentoxifylline) has been reported in children and adults. Symptoms appear to be dose related. A report from a poison control center on 44 patients taking overdoses of enteric-coated pentoxifylline tablets noted that symptoms usually occurred 4-5 hours after ingestion and lasted about 12 hours. The highest amount ingested was 80 mg/kg; flushing, hypotension, convulsions, somnolence, loss of consciousness, fever, and agitation occurred. All patients recovered.
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DOSAGE AND ADMINISTRATION:
The usual dosage of Trental® (pentoxifylline) in controlled-release tablet form is one tablet (400 mg) three times a day with meals.
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The Western Journal of Medicine

(ISSN 0093-0415/USPS 084 480) is published monthly for $35 per year (USA and Canada) by the California Medical Association, 221 Main Street, San Francisco, CA 94105. Second-class postage paid at San Francisco and additional mailing offices.

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Cream 0.1%
Ointment 0.1%
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INDICATIONS AND USAGE ELOCON **Cream, Ointment,** and **Lotion,** are indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

CONTRAINDICATIONS ELOCON **Cream, Ointment,** and **Lotion,** are contraindicated in patients who are hypersensitive to mometasone furoate, to other corticosteroids, or to any ingredient in these preparations.

PRECAUTIONS **General:** Systemic absorption of potent topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients.

Conditions which augment systemic absorption include application of more potent steroids, application of steroids in optimized vehicles, use over large surface areas, prolonged use, use in areas where the epidermal barrier is disrupted, and the use of occlusive dressings. (See **DOSAGE AND ADMINISTRATION.**)

Patients receiving a large dose of a potent topical steroid applied to a large surface area or under an occlusive dressing should be evaluated periodically for evidence of HPA axis suppression by using the urinary free cortisol and ACTH stimulation tests. If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid.

Recovery of HPA axis function is generally prompt and complete upon discontinuation of the drug. Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids.

Children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity. (See **PRECAUTIONS – Pediatric Use.**)

If irritation develops, topical corticosteroids should be discontinued and appropriate therapy instituted.

In the presence of dermatological infections, use of an appropriate antifungal or antibacterial agent should be instituted. If a favorable response does not occur promptly, the corticosteroid should be discontinued until the infection has been adequately controlled.

Laboratory Tests The following tests may be helpful in evaluating HPA axis suppression:

Urinary free cortisol test
ACTH stimulation test

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Long-term animal studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of topical corticosteroids.

Genetic toxicity studies with mometasone furoate, which included the Ames test, mouse lymphoma assay, and a micronucleus test, did not reveal any mutagenic potential.

Pregnancy Category C: Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. There are no adequate and well-controlled studies of teratogenic effects from topically applied corticosteroids in pregnant women. Therefore, topical corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods.

Nursing Mothers: It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids are secreted into breast milk in quantities not likely to have a deleterious effect on the infant. Nevertheless, a decision should be made whether to discontinue nursing or to discontinue the drug taking into account the importance of the drug to the mother.

Pediatric Use: *Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced HPA axis suppression and Cushing's syndrome than mature patients because of a larger skin surface area to body weight ratio.*

Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children.

ADVERSE REACTIONS The following local adverse reactions were reported with ELOCON **Cream** during clinical studies with 319 patients: burning, 1; pruritus, 1; and signs of skin atrophy, 3.

The following local adverse reactions were reported with ELOCON **Ointment** during clinical studies with 812 patients: burning, 13; pruritus, 8; skin atrophy, 8; tingling/stinging, 7; and furunculosis, 3.

The following local adverse reactions were reported with ELOCON **Lotion** during clinical studies with 209 patients: acneiform reaction, 2; burning, 4; and itching, 1. In an irritation/sensitization study with 156 normal subjects, folliculitis was reported in 4.

The following local adverse reactions have been reported infrequently when other topical dermatologic corticosteroids have been used as recommended. These reactions are listed in an approximate decreasing order of occurrence: burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae, miliaria.

OVERDOSAGE Topically applied corticosteroids can be absorbed in sufficient amounts to produce systemic effects. (See **PRECAUTIONS.**)

DOSAGE AND ADMINISTRATION Apply a thin film of ELOCON **Cream** or **Ointment** to the affected skin areas once daily. Do not use occlusive dressings.

Apply a few drops of ELOCON **Lotion** to the affected areas once daily and massage lightly until it disappears. For the most effective and economical use, hold the nozzle of the bottle very close to the affected areas and gently squeeze.

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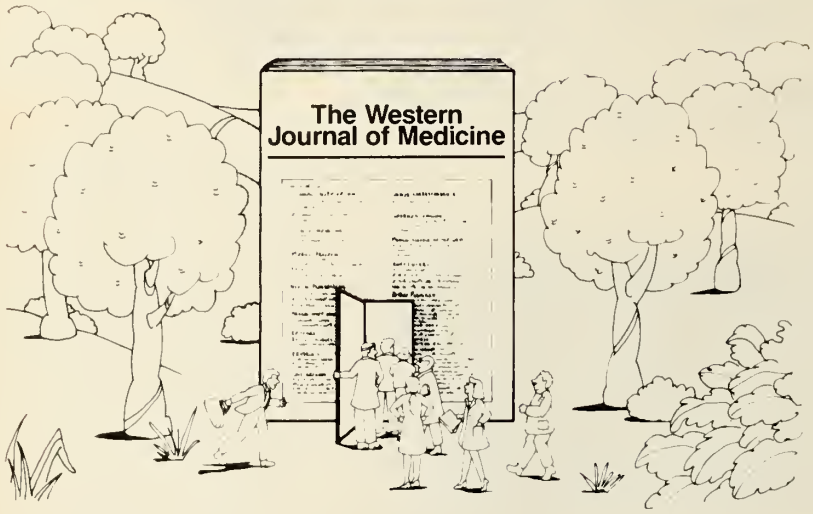

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Contraindications: *'Tagamet' is contraindicated for patients known to have hypersensitivity to the product.*

Precautions: *Rare instances of cardiac arrhythmias and hypotension have been reported following the rapid administration of 'Tagamet' (brand of cimetidine hydrochloride) Injection by intravenous bolus.*

Symptomatic response to 'Tagamet' therapy does not preclude the presence of a gastric malignancy. There have been rare reports of transient healing of gastric ulcers despite subsequently documented malignancy.

Reversible confusional states have been observed on occasion, predominantly in severely ill patients.

'Tagamet' has been reported to reduce the hepatic metabolism of warfarin-type anticoagulants, phenytoin, propranolol, chlordiazepoxide, diazepam, certain tricyclic antidepressants, lidocaine, theophylline and metronidazole. Clinically significant effects have been reported with the warfarin anticoagulants; therefore, close monitoring of prothrombin time is recommended, and adjustment of the anticoagulant dose may be necessary when 'Tagamet' is administered concomitantly. Interaction with phenytoin, lidocaine and theophylline has also been reported to produce adverse clinical effects.

However, a crossover study in healthy subjects receiving either 'Tagamet' 300 mg q.i.d. or 800 mg h.s. concomitantly with a 300 mg b.i.d. dosage of theophylline (Theo-Dur®, Key Pharmaceuticals, Inc.) demonstrated less alteration in steady-state theophylline peak serum levels with the 800 mg h.s. regimen, particularly in subjects aged 54 years and older. Data beyond ten days are not available. (Note: All patients receiving theophylline should be monitored appropriately, regardless of concomitant drug therapy.)

In a 24-month toxicity study in rats, at dose levels approximately 8 to 48 times the recommended human dose, benign Leydig cell tumors were seen. These were common in both the treated and control groups, and the incidence became significantly higher only in the aged rats receiving 'Tagamet'.

A weak antiandrogenic effect has been demonstrated in animals. In human studies, 'Tagamet' has been shown to have no effect on spermatogenesis, sperm count, motility, morphology or in vitro fertilizing capacity.

Pregnancy Category B: Reproduction studies have been performed in rats, rabbits and mice at doses up to 40 times the normal human dose and have revealed no evidence of impaired fertility or harm to the fetus due to 'Tagamet'. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Lack of experience to date precludes recommending 'Tagamet' for use in children under 16 unless anticipated benefits outweigh potential risks; generally, nursing should not be undertaken by patients taking the drug since cimetidine is secreted in human milk.

Adverse Reactions: *Diarrhea, dizziness, somnolence, headache. Reversible confusional states (e.g., mental confusion, agitation, psychosis, depression, anxiety, hallucinations, disorientation), predominantly in severely ill patients, have been reported. Reversible impotence in patients with pathological hypersecretory disorders receiving 'Tagamet', particularly in high doses for at least 12 months, has been reported. The incidence of impotence in large-scale surveillance studies at regular doses has not exceeded that commonly reported in the general population. Gynecomastia has been reported in patients treated for one month or longer. Decreased white blood cell counts in 'Tagamet'-treated patients (approximately 1 per 100,000 patients), including agranulocytosis (approximately 3 per million patients), have been reported, including a few reports of recurrence on rechallenge. Most of these reports were in patients who had serious concomitant illnesses and received drugs and/or treatment known to produce neutropenia. Thrombocytopenia (approximately 3 per million patients) and, very rarely, cases of aplastic anemia have also been reported. Increased serum transaminase has been reported. Reversible adverse hepatic effects, cholestatic or mixed cholestatic-hepatocellular in nature, have been reported rarely. Because of the predominance of cholestatic features, severe parenchymal injury is considered highly unlikely. A single case of biopsy-proven periportal hepatic fibrosis in a patient receiving 'Tagamet' has been reported. Increased plasma creatinine has been reported. Rare cases of fever, interstitial nephritis, urinary retention, pancreatitis and allergic reactions, including anaphylaxis and hypersensitivity vasculitis, have been reported. Rare cases of bradycardia, tachycardia and A-V heart block have been reported with H_2-receptor antagonists. Reversible arthralgia, myalgia and exacerbation of joint symptoms in patients with pre-existing arthritis have been reported rarely. Rare cases of polymyositis have been reported, but no causal relationship has been established. Mild rash and, very rarely, cases of severe generalized skin reactions (e.g., Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme, exfoliative dermatitis and generalized exfoliative erythroderma) have been reported with H_2-receptor antagonists. Reversible alopecia has been reported very rarely.*

How Supplied: Tablets: *200 mg tablets in bottles of 100; 300 mg tablets in bottles of 100 and Single Unit Packages of 100 (intended for institutional use only); 400 mg tablets in bottles of 60 and Single Unit Packages of 100 (intended for institutional use only), and 800 mg Tiltab® tablets in bottles of 30 and Single Unit Packages of 100 (intended for institutional use only).*

Liquid: *300 mg/5 mL, in 8 fl oz (237 mL) amber glass bottles and in single-dose units (300 mg/5 mL), in packages of 10 (intended for institutional use only).*

Injection:
Vials: *300 mg/2 mL in single-dose vials, in packages of 10 and 30, and in 8 mL multiple-dose vials, in packages of 10 and 25.*

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Single-Dose Premixed Plastic Containers: *300 mg in 50 mL of 0.9% Sodium Chloride in single-dose plastic containers, in packages of 4 units. No preservative has been added.*

Exposure of the premixed product to excessive heat should be avoided. It is recommended the product be stored at controlled room temperature. Brief exposure up to 40°C does not adversely affect the premixed product.

ADD-Vantage® Vials: *300 mg/2 mL in single-dose ADD-Vantage® Vials, in packages of 25.*

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641 **The Biology and Physiology of Aging**

Discussant: ITAMAR B. ABRASS, MD

A discussion selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from a transcription, it was edited by Homer A. Boushey, MD, Professor of Medicine, and Nathan M. Bass, MD, PhD, Associate Professor of Medicine, under the direction of Lloyd H. Smith, Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine.

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Pediatrics

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646 **Diagnosis, Treatment, and Follow-up of Newborns Addicted to Cocaine**

ROBIN L. HANSEN, MD

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References: 1. Newton RE, *et al.* A review of the side effect profile of buspirone. *Am J Med* 1986;80(3B):17-21. 2. Lucki I, *et al.* Differential effects of the anxiolytic drugs, diazepam and buspirone, on memory function. *Br J Clin Pharmacol* 1987;23:207-211. 3. Lader M. Assessing the potential for buspirone dependence or abuse and effects of its withdrawal. *Am J Med* 1987;82(5A):20-26.

Contraindications: Hypersensitivity to buspirone hydrochloride.

Warnings: The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. Since blood pressure has become elevated when BuSpar was administered concomitantly with an MAOI, such concomitant use is not recommended. BuSpar should not be employed in lieu of appropriate antipsychotic treatment.

Precautions: General—*Interference with cognitive and motor performance:* Although buspirone is less sedating than other anxiolytics and does not produce significant functional impairment, its CNS effects in a given patient may not be predictable; therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone does not affect them adversely. Although buspirone has not been shown to increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use with alcohol.

Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug dependent patients: Because buspirone will not block the withdrawal syndrome often seen with cessation of therapy with benzodiazepines and other common sedative/hypnotic drugs, before starting buspirone withdraw patients gradually from their prior treatment, especially those who used a CNS depressant chronically. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug and its elimination half-life. The withdrawal syndrome can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

Possible concerns related to buspirone's binding to dopamine receptors: Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (eg, dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported; the syndrome may be due to increased central noradrenergic activity or may be attributable to dopaminergic effects (ie, represent akathisia).

Information for Patients—Patients should be instructed to inform their physician about any medications, prescription or nonprescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone, to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone; to inform their physician if they are breast feeding; and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them.

Drug Interactions—Concomitant use with other CNS active drugs should be approached with caution (see **Warnings**). Concomitant use with trazodone may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients. Concomitant administration of BuSpar and haloperidol resulted in increased serum haloperidol concentrations in normal volunteers. The clinical significance is not clear. Buspirone does not displace tightly bound drugs like phenytoin, propranolol, and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin. However, there was one report of prolonged prothrombin time when buspirone was given to a patient also treated with warfarin, phenytoin, phenobarbital, digoxin, and Synthroid.

Carcinogenesis, Mutagenesis, Impairment of Fertility—No evidence of carcinogenic potential was observed in rats or mice; buspirone did not induce point mutations, nor was DNA damage observed; chromosomal aberrations or abnormalities did not occur.

Pregnancy: Teratogenic Effects—Pregnancy Category B: Should be used during pregnancy only if clearly needed.

Nursing Mothers—Administration to nursing women should be avoided if clinically possible.

Pediatric Use—The safety and effectiveness have not been determined in individuals below 18 years of age.

Use in the Elderly—No unusual, adverse, age-related phenomena have been identified in elderly patients receiving a total, modal daily dose of 15 mg.

Use in Patients with Impaired Hepatic or Renal Function—Since buspirone is metabolized by the liver and excreted by the kidneys, it is not recommended in severe hepatic or renal impairment.

Adverse Reactions (See also Precautions): *Commonly Observed*—The more commonly observed untoward events, not seen at an equivalent incidence in placebo-treated patients, include dizziness, nausea, headache, nervousness, lightheadedness, and excitement.

Associated with Discontinuation of Treatment—The more common events causing discontinuation included: central nervous system disturbances (3.4%), primarily dizziness, insomnia, nervousness, drowsiness, lightheaded feeling; gastrointestinal disturbances (1.2%), primarily nausea; miscellaneous disturbances (1.1%), primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary.

Incidence in Controlled Clinical Trials—Adverse events reported by 1% or more of 477 patients who received buspirone in four-week, controlled trials: *Cardiovascular:* Tachycardia/palpitations 1%. *CNS:* Dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, lightheadedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2%. *EENT:* Blurred vision 2%. *Gastrointestinal:* Nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1%. *Musculoskeletal:* Musculoskeletal aches/pains 1%. *Neurological:* Numbness 2%, paresthesia 1%, incoordination 1%, tremor 1%. *Skin:* Skin rash 1%. *Miscellaneous:* Headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%.

Other Events Observed During the Entire Premarketing Evaluation—The relative frequency of all other undesirable events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under well-controlled, open, and uncontrolled conditions is defined as follows: Frequent are those occurring in at least 1/100 patients; infrequent are those occurring in 1/100 to 1/1000 patients, and rare are those occurring in less than 1/1000 patients. *Cardiovascular*—frequent: nonspecific chest pain; infrequent: syncope, hypotension, hypertension; rare: cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, bradycardia. *Central Nervous System*—frequent: dream disturbances, infrequent: depersonalization, dysphoria, noise intolerance, euphoria, akathisia, fearfulness, loss of interest, dissociative reaction, hallucinations, suicidal ideation, seizures; rare: feelings of claustrophobia, cold intolerance, stupor, slurred speech, psychosis. *EENT*—frequent: tinnitus, sore throat, nasal congestion; infrequent: redness and itching of the eyes, altered taste, altered smell, conjunctivitis; rare: inner ear abnormality, eye pain, photophobia, pressure on eyes. *Endocrine*—rare: galactorrhea, thyroid abnormality. *Gastrointestinal*—infrequent: flatulence, anorexia, increased appetite, salivation, irritable colon, rectal bleeding; rare: burning of the tongue. *Genitourinary*—infrequent: urinary frequency, urinary hesitancy, menstrual irregularity and spotting, dysuria; rare: amenorrhea, pelvic inflammatory disease, enuresis, nocturia. *Musculoskeletal*—infrequent: muscle cramps, muscle spasms, rigid/stiff muscles, arthralgias. *Neurological*—infrequent: involuntary movements, slowed reaction time; rare: muscle weakness. *Respiratory*—infrequent: hyperventilation, shortness of breath, chest congestion; rare: epistaxis. *Sexual Function*—infrequent: decreased or increased libido; rare: delayed ejaculation, impotence. *Skin*—infrequent: edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema, blisters; rare: acne, thinning of nails. *Clinical Laboratory*—infrequent: increases in hepatic aminotransferases (SGOT, SGPT); rare: eosinophilia, leukopenia, thrombocytopenia. *Miscellaneous*—infrequent: weight gain, fever, roaring sensation in the head, weight loss, malaise; rare: alcohol abuse, bleeding disturbance, loss of voice, hiccoughs.

Postintroduction Clinical Experience—Rare occurrences of allergic reactions, cogwheel rigidity, dystonic reactions, ecchymosis, emotional lability, tunnel vision, and urinary retention have been reported. Because of the uncontrolled nature of these spontaneous reports, a causal relationship to BuSpar has not been determined.

Drug Abuse and Dependence: *Controlled Substance Class*—Not a controlled substance.

Physical and Psychological Dependence—Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. However, since it is difficult to predict from experiments the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (eg, development of tolerance, incrementation of dose, drug-seeking behavior).

Overdosage: *Signs and Symptoms*—At doses approaching 375 mg/day the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. No deaths have been reported in humans either with deliberate or accidental overdosage.

Recommended Overdose Treatment—General symptomatic and supportive measures should be used along with immediate gastric lavage. No specific antidote is known and dialyzability of buspirone has not been determined.

For complete details, see Prescribing Information or consult your Mead Johnson Pharmaceuticals Representative.

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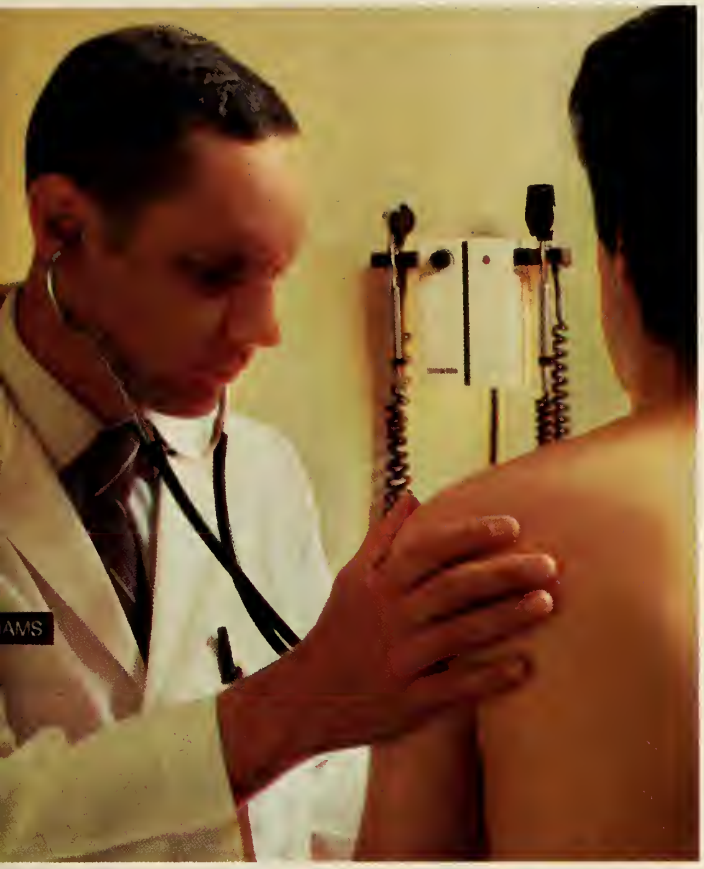

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ARTHUR L. M. SWISLOCKI, MD; CARLOS A. CAMARGO, MD; and ANDREW R. HOFFMAN, MD

From the Geriatric Research, Education, and Clinical Center, Veterans Administration Medical Center, Palo Alto, and the Division of Endocrinology, Department of Medicine, Stanford University School of Medicine, Stanford, California. Dr Swislocki is currently with the Medical Service, Veterans Administration Medical Center, Martinez, California, and the Division of Endocrinology, Department of Medicine, University of California, Davis, School of Medicine.

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JOHN D. GASMAN, MD; JOSEPH VARON, MD; and JAMES P. GARDNER, MD

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MARIA LEISA C. MAGBOO, MD, and ORLO H. CLARK, MD

From the Metabolic Research Unit and the Department of Surgery, University of California, San Francisco, School of Medicine, and the Department of Surgery, Veterans Administration Medical Center, San Francisco.

EDITORIALS

660 Parathyroid Hormone-Related Peptide
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inhaler

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Brief Summary

DESCRIPTION: Azmacort (triamcinolone acetonide) is an anti-inflammatory steroid.

INDICATIONS: Azmacort (triamcinolone acetonide) inhaler is indicated only for patients who require chronic treatment with corticosteroids for the control of the symptoms of bronchial asthma. Such patients would include those already receiving systemic corticosteroids and selected patients who are inadequately controlled on a non-steroid regimen and in whom steroid therapy has been withheld because of concern over potential adverse effects.

Azmacort inhaler is *NOT* indicated:
1. For relief of asthma which can be controlled by bronchodilators and other non-steroid medications.
2. In patients who require systemic corticosteroid treatment infrequently
3. In the treatment of non-asthmatic bronchitis.

CONTRAINDICATIONS: Azmacort inhaler is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

Hypersensitivity to any of the ingredients of this preparation contraindicates its use.

WARNINGS: Particular care is needed in patients who are transferred from systemically active corticosteroids to Azmacort inhaler because deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to aerosolized steroids in recommended doses. After withdrawal from systemic corticosteroids, a number of months is usually required for recovery of hypothalamic-pituitary-adrenal (HPA) function. For some patients who have received large doses of oral steroids for long periods of time before therapy with Azmacort inhaler is initiated, recovery may be delayed for one year or longer. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery or infections, particularly gastroenteritis or other conditions with acute electrolyte loss. Although Azmacort inhaler may provide control of asthmatic symptoms during these episodes, in recommended doses it supplies only normal physiological amounts of corticosteroid systemically and does NOT provide the increased systemic steroid which is necessary for coping with these emergencies.

During periods of stress or a severe asthmatic attack, patients who have been recently withdrawn from systemic corticosteroids should be instructed to resume systemic steroids (in large doses) immediately and to contact their physician for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic steroids during periods of stress or a severe asthma attack.

Localized infections with *Candida albicans* have occurred infrequently in the mouth and pharynx. These areas should be examined by the treating physician at each patient visit. The percentage of positive mouth and throat cultures for *Candida albicans* did not change during a year of continuous therapy. The incidence of clinically apparent infection is low (2.5%). These infections may disappear spontaneously or may require treatment with appropriate antifungal therapy or discontinuance of treatment with Azmacort inhaler.

Azmacort inhaler is not to be regarded as a bronchodilator and is not indicated for rapid relief of bronchospasm.

Patients should be instructed to contact their physician immediately when episodes of asthma which are not responsive to bronchodilators occur during the course of treatment with Azmacort inhaler. During such episodes, patients may require therapy with systemic corticosteroids.

There is no evidence that control of asthma can be achieved by the administration of Azmacort inhaler in amounts greater than the recommended doses, which appear to be the therapeutic equivalent of approximately 10 mg/day of oral prednisone.

Theoretically, the use of inhaled corticosteroids with alternate day prednisone oral therapy should be accompanied by more HPA suppression than a therapeutically equivalent regimen of either alone.

Transfer of patients from systemic steroid therapy to Azmacort inhaler may unmask allergic conditions previously suppressed by the systemic steroid therapy, e.g., rhinitis, conjunctivitis, and eczema.

PRECAUTIONS: During withdrawal from oral steroids, some patients may experience symptoms of systemically active steroid withdrawal, e.g., joint and/or muscular pain, lassitude and depression, despite maintenance or even improvement of respiratory function (See DOSAGE AND ADMINISTRATION for details). Although steroid withdrawal effects are usually transient and not severe, severe and even fatal exacerbation of asthma can occur if the previous daily oral corticosteroid requirement had significantly exceeded 10 mg/day of prednisone or equivalent.

In responsive patients, inhaled corticosteroids will often permit control of asthmatic symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since triamcinolone acetonide is absorbed into the circulation and can be systemically active, the beneficial effects of Azmacort inhaler in minimizing or preventing HPA dysfunction may be expected only when recommended dosages are not exceeded.

Suppression of HPA function has been reported in volunteers who received 4000 mcg daily of triamcinolone acetonide. In addition, suppression of HPA function has been reported in some patients who have received recommended doses for as little as 6-12 weeks. Since the response of HPA function to inhaled corticosteroids is highly individualized, the physician should consider this information when treating patients.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with these drugs should be observed carefully for any evidence of systemic corticosteroid effects including suppression of growth in children. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of a decrease in adrenal function.

The long-term effects of triamcinolone acetonide inhaler in human subjects are not completely known, although patients have received Azmacort inhaler on a continuous basis for periods of two years or longer. While there has been no clinical evidence of adverse experiences, the local effects of the agent on developmental or immunologic processes in the mouth, pharynx, trachea and lung are also unknown.

The potential effects of Azmacort inhaler on acute, recurrent, or chronic pulmonary infections, including active or quiescent tuberculosis, are not known. For this reason, since systemic administration of corticosteroids may mask some signs of fungal, bacterial or viral infection, the same caution should be observed when treating patients with Azmacort inhaler. The potential effects of long-term administration of Azmacort inhaler on lung or other tissues are unknown. However, pulmonary infiltrates with eosinophilia have occurred in patients receiving other inhaled corticosteroids.

Pregnancy: Pregnancy Category C: Azmacort (triamcinolone acetonide) has been shown to be teratogenic in rats and rabbits when given in doses comparable to the highest dose recommended for human use (approximately 0.032 mg/kg/day). Administration of aerosol inhalation to pregnant rats and rabbits produced embryotoxic and tetotoxic effects which were comparable to those produced by administration by other routes.

Teratogenic effects in both species included a low incidence of cleft palate and/or internal hydrocephaly and axial skeletal defects. These findings represent known effects of glucocorticoids in laboratory animals.

There are no well-controlled studies in pregnant women. Experience with other dosage forms of triamcinolone acetonide does not include any positive evidence of adverse effects on the fetus. However, since such experience cannot exclude possibility of fetal damage, Azmacort inhaler should be used during pregnancy only if the benefit clearly justifies the potential risk to the fetus. Infants born to mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for hypoadrenalism.

Nursing mothers: It is not known whether this drug is excreted in human milk. Because of the potential for tumorigenicity shown for triamcinolone acetonide in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

ADVERSE REACTIONS: A few cases of oral candidiasis have been reported (see WARNINGS). In addition, some patients receiving Azmacort inhaler have experienced hoarseness, dry throat, irritated throat and dry mouth. Increased wheezing and cough have been reported infrequently as has facial edema. These adverse effects have generally been mild and transient.

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Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalmic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon® is indicated as a sympathicolytic and mydriatic. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.[1,2] Also dizziness, headache, skin flushing reported when used orally.[1,3]

Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.[1,3,4] 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to ½ tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.[3]

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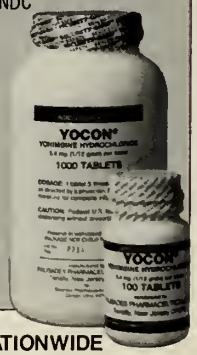

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4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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★ Official Journal of the Alaska State Medical Association, the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

★ Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.

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In Memoriam

California Medical Association

Baxter, John W., Los Altos. Died Sep 27, 1990, aged 61. Graduate of Bowman Gray School of Medicine, Winston-Salem, North Carolina, 1957. Dr Baxter was a member of the Santa Clara County Medical Association.

Bradman, Bernard, Kentfield. Died Sep 20, 1990, aged 66. Graduate of University of Geneva, Switzerland, 1958. Licensed in California in 1960. Dr Bradman was a member of the Marin Medical Society.

Christensen, Burt H., Oakland. Died May 31, 1990, aged 72. Graduate of Johns Hopkins University School of Medicine, Baltimore, Maryland, 1938. Licensed in California in 1943. Dr Christensen was a member of the Alameda-Contra Costa Medical Association.

Cohen, Jeffrey Lewis, San Francisco. Died Oct 4, 1990, aged 38. Graduate of University of California, San Francisco, 1979. Licensed in California in 1980. Dr Cohen was a member of the San Francisco Medical Society.

Edmister, Ivan F., Martinez. Died Jun 22, 1990, aged 82. Graduate of University of California, San Francisco, 1944. Dr Edmister was a member of the Alameda-Contra Costa Medical Association.

Ellenberger, Lester E., Colton. Died July 2, 1990, aged 82. Graduate of College of Medical Evangelists, 1937. Licensed in California in 1938. Dr Ellenberger was a member of the San Bernardino County Medical Society.

Farrelly, Laurence D., Visalia. Died Sep 4, 1990, aged 72. Graduate of University of Manitoba, Winnipeg, Canada, 1953. Licensed in California in 1953. Dr Farrelly was a member of the Tulare County Medical Society.

Fien, Irving, Concord. Died Sep 17, 1990, aged 74. Graduate of Stanford Medical School, Stanford, California, 1944. Licensed in California in 1950. Dr Fien was a member of the Alameda-Contra Costa Medical Association.

Hambrick, Edward, San Francisco. Died Oct 7, 1990, aged 72. Graduate of Meharry Medical College, Nashville, Tennessee, 1944. Licensed in California in 1945. Dr Hambrick was a member of the San Francisco Medical Society.

Hunter, James M., Ventura. Died Oct 10, 1990, aged 71. Graduate of University of Louisville School of Medicine, Louisville, Kentucky, 1943. Dr Hunter was a member of the Ventura County Medical Society.

Karp, H. Neil, Santa Barbara. Died Aug 14, 1990, aged 65. Graduate of Ohio State University, Columbus, 1949. Licensed in California in 1951. Dr Karp was a member of the Santa Barbara County Medical Society.

Lopez, Vincent G., Lamont. Died Oct 12, 1990, aged 69. Graduate of Stanford University, Stanford, California, 1957. Dr Lopez was a member of the Kern County Medical Society.

Madsen, Karl P. B., Oakland. Died Aug 22, 1990, aged 88. Graduate of California College of Medicine, 1962. Licensed in California in 1975. Dr Madsen was a member of the Alameda-Contra Costa Medical Association.

Mead, James G., Hemet. Died Aug 4, 1990, aged 76. Graduate of Loma Linda University, Loma Linda, California, 1940. Licensed in California in 1946. Dr Mead was a member of the Riverside County Medical Association.

Modglin, F. Rene, Rancho Cucamonga. Died Aug 6, 1990, aged 70. Graduate of Loma Linda University, Loma Linda, California, 1947. Licensed in California in 1948. Dr Modglin was a member of the Riverside County Medical Association.

Myers, Helen S., Berkeley. Died Aug 20, 1990, aged 72. Graduate of George Washington University, Washington, DC, 1947. Licensed in California in 1949.

Pelkey, George L., San Bernardino. Died Sep 5, 1990, aged 78. Graduate of Rush Medical College of University of Chicago, 1938. Licensed in California in 1946. Dr Pelkey was a member of the San Bernardino County Medical Society.

Perloff, William H., Santa Barbara. Died Aug 29, 1990, aged 79. Graduate of University of Pennsylvania, Philadelphia, 1936. Licensed in California in 1966. Dr Perloff was a member of the Santa Barbara County Medical Society.

Petersen, Breck J., San Bernardino. Died Sep 8, 1990, aged 58. Graduate of California College of Medicine, 1962. Dr Petersen was a member of the San Bernardino County Medical Society.

Potter, Robert W., Fresno. Died Oct 11, 1990, aged 68. Graduate of New York University School of Medicine, 1951. Licensed in California in 1952. Dr Potter was a member of the Fresno-Madera Medical Society.

Shapero, Alvin A., Anaheim. Died Sep 2, 1990, aged 63. Graduate of University of California, Irvine, 1965. Licensed in California in 1966. Dr Shapero was a member of the Orange County Medical Association.

Shea, Lawrence P., San Mateo. Died Feb 13, 1990, aged 67. Graduate of Yale University School of Medicine, New Haven, Connecticut, 1947. Licensed in California in 1968. Dr Shea was a member of the San Mateo County Medical Society.

Vandermeer, Billy Lee, Sacramento. Died Aug 2, 1990, aged 64. Graduate of University of Utah, Salt Lake City, 1952. Dr Vandermeer was a member of the Sacramento-El Dorado Medical Society.

Idaho Medical Association

Almer, Lennart E., Boise. Died May 18, 1990, aged 83. Graduate of University of Nebraska, Omaha, 1937. Licensed in Idaho in 1970. Dr Almer was a member of the Ada County Medical Society.

Crawford, Howard W., Rupert. Died Apr 5, 1990, aged 72. Graduate of University of Colorado, Boulder, 1950. Licensed in Idaho in 1956. Dr Crawford was a member of the Mini-Cassia District Medical Society.

Simpson, Samuel Dixon, Caldwell. Died Jun 20, 1990, aged 78. Graduate of University of Texas Medical School, Galveston, 1939. Licensed in Idaho in 1940. Dr Simpson was a member of the Southwestern Idaho District Medical Society.

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See adjacent page for Brief Summary of Product Information

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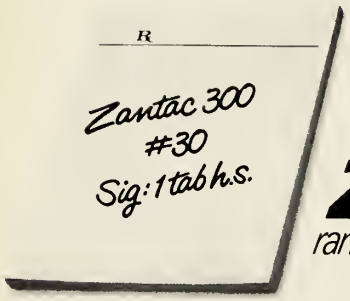

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Zantac® 150 Tablets
(ranitidine hydrochloride)

Zantac® 300 Tablets
(ranitidine hydrochloride)

Zantac® Syrup
(ranitidine hydrochloride)

BRIEF SUMMARY

The following is a brief summary only. Before prescribing, see complete prescribing information in Zantac® product labeling.

INDICATIONS AND USAGE: Zantac® is indicated in:
1. Short-term treatment of **active duodenal ulcer.** Most patients heal within four weeks.
2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathological hypersecretory conditions** (eg, Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of **active, benign gastric ulcer.** Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated.
5. Treatment of **gastroesophageal reflux disease (GERD).** Symptomatic relief commonly occurs within one or two weeks after starting therapy. Therapy for longer than six weeks has not been studied.

In active duodenal ulcer; active, benign gastric ulcer; hypersecretory states; and GERD, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: Zantac® is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS:

General: 1. Symptomatic response to Zantac® therapy does not preclude the presence of gastric malignancy.
2. Since Zantac is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since Zantac is metabolized in the liver.

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during Zantac therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although Zantac has been reported to bind weakly to cytochrome P-450 *in vitro*, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions that suggest that Zantac may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2,000 mg/kg/d.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, Escherichia coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Zantac. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Zantac is secreted in human milk. Caution should be exercised when Zantac is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with Zantac®. The relationship to Zantac therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to Zantac administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported.

Cardiovascular: As with other H_2-blockers, rare reports of arrhythmias such as tachycardia, bradycardia, atrioventricular block, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, abdominal discomfort/pain, and rare reports of pancreatitis.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid intravenously for seven days, and in 4 of 24 subjects receiving 50 mg qid intravenously for five days. There have been occasional reports of hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice. In such circumstances, ranitidine should be immediately discontinued. These events are usually reversible, but in exceedingly rare circumstances death has occurred.

Zantac® 150 and 300 (ranitidine hydrochloride) Tablets
Zantac® (ranitidine hydrochloride) Syrup

Musculoskeletal: Rare reports of arthralgias.

Hematologic: Blood count changes (leukopenia, granulocytopenia, thrombocytopenia) have occurred in a few patients. These were usually reversible. Rare cases of agranulocytosis, pancytopenia, sometimes with marrow hypoplasia, and aplastic anemia have been reported.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by Zantac and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when Zantac has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving Zantac, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia), anaphylaxis, angioneurotic edema, and small increases in serum creatinine.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: (See complete prescribing information in Zantac® product labeling).

Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice daily. An alternate dosage of 300 mg or 20 ml (4 teaspoonfuls equivalent to 300 mg of ranitidine) once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.

Maintenance Therapy: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day. In some patients it may be necessary to administer Zantac® 150-mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/d have been employed in patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day.

GERD: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day.

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with Zantac, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: Zantac® 300 Tablets (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 (NDC 0173-0393-40) tablets and unit dose packs of 100 (NDC 0173-0393-47) tablets.

Zantac® 150 Tablets (ranitidine hydrochloride equivalent to 150 mg of ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 60 (NDC 0173-0344-42) and 100 (NDC 0173-0344-09) tablets and unit dose packs of 100 (NDC 0173-0344-47) tablets.

Store between 15° and 30° C (59° and 86° F) in a dry place. Protect from light. Replace cap securely after each opening.

Zantac® Syrup, a clear, peppermint-flavored liquid, contains 16.8 mg of ranitidine hydrochloride equivalent to 15 mg of ranitidine per 1 ml in bottles of 16 fluid ounces (one pint) (NDC 0173-0383-54).

Store between 4° and 25° C (39° and 77° F). Dispense in tight, light-resistant containers as defined in the USP/NF.

July 1990

Glaxo Pharmaceuticals
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Research Triangle Park, NC 27709

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SPECIAL ISSUES

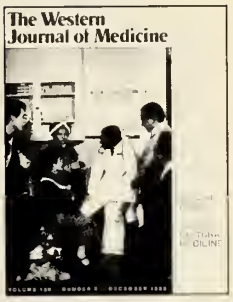
Addiction Medicine
and the Primary Care Physician

Addiction Medicine and the Primary Care Physician was conceived to be part of the initiative to expand the involvement of all specialties of medicine in the prevention and treatment of addictive disease. Topics covered include chemical dependence and the workplace, alcoholism, methadone maintenance in the treatment of opioid dependence, nicotine dependence, and treatment of cocaine dependence. David Smith MD, Special Editor, 1990.

Women and Medicine

This special issue explores both the professional side of women in medicine and the diagnosis and treatment of women patients. Topics covered include liver disease, women and AIDS, heart disease, hysterectomy, PMS, ovarian cancer, and women physicians and organized medicine. Linda Hawes Clever, MD, Special Issue Editor, 1988.

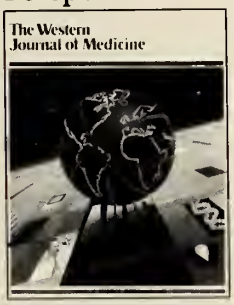
Cross-cultural Medicine



Cross-cultural medicine is devoted to the care of patients of different cultural, ethnic, or religious backgrounds. Subjects include Southeast Asian refugees in the American health care system, psychiatry and Chinese culture, health and illness in Filipino immigrants, and health care of Middle Eastern patients. M. Margaret Clark, PhD, Special Issue Editor, 1983. 2nd reprinted edition.

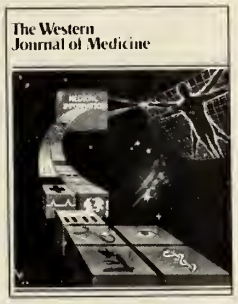
Also available:

AIDS—A Global Perspective



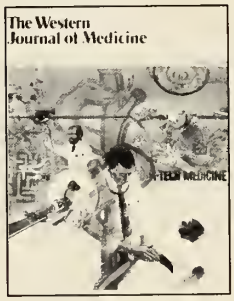
Jonathan M. Mann, MD
Special Issue Editor, 1987

Medical Informatics



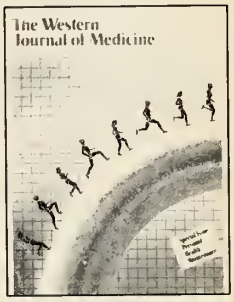
Marsden S. Blois, MD
Special Issue Editor, 1986

High-Tech Medicine



R. Paul Robertson, MD
Special Issue Editor, 1985

Personal Health Maintenance



John H. Holbrook, MD
Special Issue Editor, 1984

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ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

January 19—**Current Topics in Anesthesia.** Mayo Clinic-Scottsdale. Sat. Contact: Trish Gean, (602) 391-8300.

January 26—**Current Issues in Nephrology and Hypertension.** Ashton B. Taylor Auditorium, Mayo Clinic-Scottsdale. Sat. Contact: Mayo Clinic-Scottsdale.

February 15-17—**Anesthesia for the '90s: 17th Annual Scientific Meeting.** Arizona Society of Anesthesiologists at Wyndham Paradise Valley Resort, Paradise Valley. Fri-Sun. Contact: Beverly Reichter, (602) 246-8901.

February 21-23—**17th Annual Frontiers in Ophthalmology.** St Luke's Medical Center at Red Lion's La Posada Resort, Scottsdale. Thurs-Sat. Contact: Christine Campbell, (602) 820-7027.

February 28-March 2—**13th Annual Postgraduate Course: Advances in Obstetrics and Gynecology.** Maricopa Medical Center and Phoenix OB/GYN Society at the Scottsdale Hilton Hotel, Scottsdale. Thurs-Sat. Contact: (602) 266-6321.

February 28-March 3—**Arizona Academy of Family Physicians Annual Scientific Assembly.** Scottsdale Plaza Resort. Thurs-Sun. Contact: Nancy Reeves, (602) 249-2021.

March 2—**ENT for the Primary Care Physician.** Ashton B. Taylor Auditorium, Mayo Clinic-Scottsdale. Sat. Contact: Mayo Clinic-Scottsdale.

March 16-20—**Fifth Annual Magnetic Resonance Imaging Conference.** Barrow Neurological Institute at Marriott's Camelback Inn, Scottsdale. Sat-Wed. Contact: Kevin King, RT, (602) 285-3956.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Jodi Lee Smith, Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 391-8300.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6707.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 541-0900. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

January 20-26—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Sheraton Hotel, Poipu Beach, Kauai. Sun-Sat. 20 hrs. $345. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

January 25-27—**29th Clinical Conference in Pediatric Anesthesiology.** Children's Hospital Pediatric Anesthesiology Foundation at Stouffer Concourse Hotel. Fri-Sun. 15 hrs. Contact: Katherine Barky, MD, PO Box 54700, Los Angeles 90054.

February 3-8—**Clinical Update in Anesthesiology.** Biennial Western Conference on Anesthesiology at Stouffer's Wailea Beach Resort, Maui, Hawaii. Sun-Fri. Contact: Murray Atnikov, MD, c/o PO Box F110-63, Blaine, WA 98230. (604) 874-5291.

March 23-24—**Case Conference in Anesthesia.** California Society of Anesthesiologists at Newport Beach Marriott. Sat-Sun. 9 hrs. $150. Contact: CSA, 1065, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (800) 345-3691.

May 16-19—**California Society of Anesthesiologist's Annual Meeting.** CSA at Marriott Hotel, Anaheim. Thurs-Sun. 20 hrs. $175. Contact: CSA, 1065, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (800) 345-3691.

CARDIOLOGY

January 24-26—**Cardiology '91.** Cardiovascular Institute at La Jolla Marriott. Thurs-Sat. Contact: Janice Turner, PO Box 2586, La Jolla 92038. (619) 459-1564.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7186.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

(Continued on Page 612)

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CONTINUING MEDICAL EDUCATION

(Continued from Page 610)

April 2-4—**1st Annual Symposium of Coronary Stenting: A Live Demonstration Course.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Tues-Thurs. 18 hrs. $750. Contact: Susan Buntjer, 400S, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

April 22-May 1—**Cardiology for the Consultant: A Physician's Retreat.** Scripps Clinic and Research Foundation at Inn Rancho Santa Fe. 1½ wks. Contact: Mary Ann Morris, 860 SW Scherer Rd, Lee's Summit, MO 64063. (816) 524-5780.

DERMATOLOGY

January 17-19—**Workshop in Dermatopathology.** Scripps Clinic and Research Foundation at Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Sat. 20 hrs. $400. Contact: Susan J Buntjer, 400S, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

January 24-26—**Cutaneous Malignancies: 1991 Skin Cancer Update.** Scripps Clinic and Research Foundation at Hyatt Regency, La Jolla. Thurs-Sat. 12 hrs. $350. Contact: Susan Buntjer, 400S, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

EMERGENCY MEDICINE

January 14-18—**Emergency Medicine Symposium I: Cardiology, Pulmonary, Neurology.** UCSD at Hyatt Regency, La Jolla. 32 hrs. $485. Contact: UCSD.

February 24-March 1—**Annual Emergency Medicine.** UCD at Hyatt Lake Tahoe, Incline Village, NV. Sun-Fri. 25 hrs. $465. Contact: UCD.

March 18-22—**Symposium II: Trauma and Surgery.** UCSD at La Jolla Marriott. Mon-Fri. 32 hrs. $485. Contact: UCSD.

April 3-6—**Advances in Emergency Medicine.** UCSF at Sheraton Palace Hotel, San Francisco. Wed-Sat. 22 hrs. $435. Contact: UCSF.

May 6-10—**Postgraduate Institute for Primary Care and Emergency Physicians Symposium I: Cardiology, Pulmonary, Neurology.** UCSD at San Diego Hilton Beach & Tennis Resort. Mon-Fri. 32 hrs. $485. Contact: UCSD.

FAMILY PRACTICE/PRIMARY CARE

January 18-20—**Practical Dermatology and Dermatologic Office Procedures for the Primary Care Physician.** UCSD at San Diego Princess Resort. Fri-Sun. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

January 26-February 2—**Vascular Update 1991.** University of Washington School of Medicine at Westin Hotel, Kauai, Hawaii. One week. Contact: U/W School of Medicine, Div of CME, SC-50, Seattle 98195. (206) 543-1050.

January 31-February 2—**Adolescent Medicine for the Practitioner.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Sat. Contact: Laurie Jones, Box 400S, Scripps Clinic, 10666 N Torrey Pines Road, La Jolla 92037. (619) 554-9592.

February 1-8—**Nevada Academy of Family Physicians Annual CME/Ski Meeting with Optional Colposcopy Certification.** NAFP at Caesars Hotel, Stateline (Lake Tahoe), Nevada. Sun-Fri. 48 hrs. Contact: Dottie Batchelor, PO Box 7471, Reno, NV 89510. (702) 826-5100.

February 11-15—**Family Practice Refresher Course.** UCI at Westin South Coast Plaza, Costa Mesa. Mon-Fri. Contact: UCI.

February 15-17—**Office Gynecology for the Primary Care Physician.** San Diego State University at Hyatt Islandia. Fri-Sun. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

February 15-18—**43rd Scientific Assembly of the California Academy of Family Physicians.** CAFP at Wyndham Hotel, Palm Springs. Fri-Mon. 23 hrs. Contact: Robert Fagan, (415) 541-0762.

February 20-23—**The Practicing Physician's Approach to the Difficult Headache Patient.** Scripps Clinic and Research Foundation and Diamond Headache Clinic at Wyndham Hotel, Palm Springs. Wed-Sat. 15 hrs. Contact: Idell Applebaum, 5252 N Western Ave, Chicago, IL 60625. (312) 878-5558.

March 15-17—**Psychopharmacology for the Primary Care Physician.** UCSD at Catamaran Resort Hotel, San Diego. Fri-Sun. Contact: Cass Jones, 7916 Convoy Ct, San Diego 92111. (619) 565-9921.

March 27-29—**Annual Review in Family Medicine: Controversies and Challenges in Primary Care.** UCSF at Cathedral Hill Hotel, San Francisco. Wed-Fri. 16 hrs. Contact: UCSF.

April 6-13—**Primary Care Medicine: Update '91.** UCSF at Waiohai Kauai, Hawaii. 1 week. 20 hrs. $525. Contact: UCSF.

April 26-28—**Office Orthopedics for the Primary Care Physician.** Sharp Memorial Hospital at San Diego Princess at Vacation Village, San Diego. Fri-Sun. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

June 10-14—**UCI Family Practice Refresher Course.** UCI at Westin South Coast Plaza, Costa Mesa. Mon-Fri. Contact: UCI.

INTERNAL MEDICINE

January 31-February 2—**Advanced Nephrology: Nephrology for the Consultant.** UCSD at Sheraton Grand Hotel, San Diego. Thurs-Sat. 17 hrs. $350. Contact: Meeting Management, 5665 Oberlin Dr, Ste 110, San Diego 92121. (619) 453-6222.

February 1-3—**8th Annual Reider Laser Symposium-Urology.** Memorial/UCI Center for Health Education at Palm Springs. Fri-Sun. Contact: UCI.

February 3-8—**Winter Urologic Forum.** UCD at Hyatt Regency Lake Tahoe, Incline Village, Nevada. Sun-Fri. 22 hrs. $400. Contact: UCD.

February 15-17—**24th Annual Recent Advances in Neurology.** UCSF at San Francisco. Fri-Sun. 15 hrs. Contact: UCSF.

February 18-20—**Clinical Hematology and Oncology: 1991.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Wed. 18 hrs. $385. Contact: Susan Buntjer, 400S, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

March 1—**17th Annual Diabetes Symposium.** UCD at Sheraton Hotel, Sacramento. Fri. 6 hrs. $140. Contact: UCD.

March 6-7—**Advances in Endocrinology and Metabolism.** UCSF at Sheraton Palace Hotel, San Francisco. Wed-Thurs. 14 hrs. $295. Contact: UCSF.

March 8-9—**Diabetes Update.** UCSF at Sheraton Palace Hotel, San Francisco. Fri-Sat. 10 hrs. $245. Contact: UCSF.

March 15-21—**Internal Medicine 1991: A Comprehensive Review.** Sharp Memorial Hospital at Hotel del Coronado, San Diego. Fri-Thurs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

May 13-17—**Advances in Internal Medicine.** UCSF at Sheraton Palace Hotel, San Francisco. Mon-Fri. 32 hrs. $585. Contact: UCSF.

OB/GYN

February 1-3—**8th Annual Reider Laser Symposium-Gynecology.** Memorial/UCI Center for Health Education at Palm Springs. Fri-Sun. Contact: UCI.

February 14-17—**46th Annual Postgraduate Assembly.** OB-GYN Assembly of Southern California at Beverly Hilton Hotel, Beverly Hills. Thurs-Sun. 28 hrs. Contact: OB-GYN Assembly, 5820 Wilshire Blvd, No. 500, Los Angeles 90036. (213) 937-5514.

March 13-17—**Gynecologic Surgery with Special Emphasis on Pre-Invasive Neoplasia and Urogynecology.** UCI/Memorial Center for Health Education at La Quinta Hotel Golf & Tennis Resort, Palm Springs. Wed-Sun. Contact: UCI.

April 10-14—**Pacific Coast Fertility Society Annual Scientific Program.** Pacific Coast Fertility Society at Stouffer Esmeralda Resort, Indian Wells. Wed-Sun. 22 hrs. Contact: Director of Medical Education, 5820 Wilshire Blvd, No 500, Los Angeles 90036. (213) 937-5514.

OCCUPATIONAL AND ENVIRONMENTAL MEDICINE

January 28-February 8—**Occupational and Environmental Medicine: Session I.** UCSF at Cathedral Hill Hotel, San Francisco. 1½ weeks. 80 hrs. $1,200. Contact: UCSF.

(Continued on Page 617)

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PRE-REGISTRATION DEADLINE: MARCH 11,1991

Registration Hotline: 800-523-1546 extension 2429 or dial direct 215-351-2429

ACP

How to Register

ACP Membership: Consult your Advance Program mailed in December, containing information about the meeting and how to register.

Non-members: Watch for the complete schedule of events and a registration form in the Annual Session Digest appearing in the December 15, 1990, and January 1 and February 1, 1991, issues of ANNALS OF INTERNAL MEDICINE.

The Western Journal of Medicine

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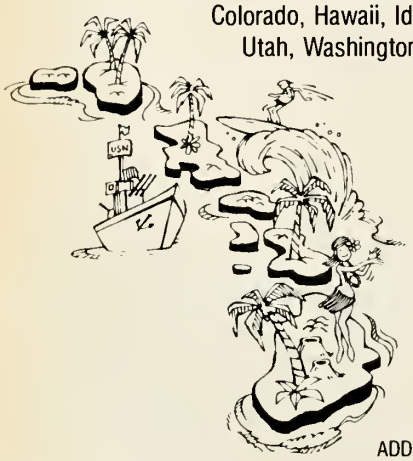
■ Enter your original medical research or medical review article—the article must be of interest to clinicians and not previously published. The winner will receive a $1,000 cash prize and a two-year subscription to **The Western Journal of Medicine.** The winning article will be published in **WJM. Deadline to enter February 1, 1991.**

■ **WJM** is the official journal of ten western medical associations and five clinical investigation/specialty societies. This competition is only open to medical students attending school in Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington, or Wyoming.



■ **WJM** is clinically oriented, national in scope, and not confined to any single specialty. Your article must be written in **WJM** style and be of interest to our readers. If, in the judgment of the editorial board, no articles meet the standards of **WJM,** no award will be made.

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■ Articles must be 3,000 to 4,000 words in length. The manuscript must be identified as submitted for consideration for this award.

■ Co-authorship is permitted if all authors meet the qualifications. The $1,000 award will be divided equally among the co-authors.

■ Articles must conform to **WJM's** style—our style guide, "Information for Authors," appears in the January and July issues, or you may write our editorial department for a copy of the guide.

■ Articles will be judged by the editors and the editorial and advisory boards of the journal.

■ The winner will be announced and the article published in **WJM.** In case of a tie, the $1,000 award will be divided equally.

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March 8 - 13, 1991

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Brief Summary.
Consult the package literature for prescribing information.
Indication: Lower respiratory infections, including pneumonia, caused by *Streptococcus pneumoniae, Haemophilus influenzae,* and *Streptococcus pyogenes* (group A β-hemolytic streptococci).
Contraindication: Known allergy to cephalosporins.
Warnings: CECLOR SHOULD BE ADMINISTERED CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. PENICILLINS AND CEPHALOSPORINS SHOW PARTIAL CROSS-ALLERGENICITY. POSSIBLE REACTIONS INCLUDE ANAPHYLAXIS.

Administer cautiously to allergic patients.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics. It must be considered in differential diagnosis of antibiotic-associated diarrhea. Colon flora is altered by broad-spectrum antibiotic treatment, possibly resulting in antibiotic-associated colitis.
Precautions:
• Discontinue Ceclor in the event of allergic reactions to it.
• Prolonged use may result in overgrowth of non-susceptible organisms.
• Positive direct Coombs' tests have been reported during treatment with cephalosporins.
• Ceclor should be administered with caution in the presence of markedly impaired renal function. Although dosage adjustments in moderate to severe renal impairment are usually not required, careful clinical observation and laboratory studies should be made.
• Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.
• Safety and effectiveness have not been determined in pregnancy, lactation, and infants less than one month old. Ceclor penetrates mother's milk. Exercise caution in prescribing for these patients.

Adverse Reactions: (percentage of patients)

Therapy-related adverse reactions are uncommon. Those reported include:
• Hypersensitivity reactions have been reported in about 1.5% of patients and include morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs' tests each occur in less than 1 in 200 patients. Cases of **serum-sickness-like** reactions have been reported with the use of Ceclor. These are characterized by findings of erythema multiforme, rashes, and other skin manifestations accompanied by arthritis/arthralgia, with or without fever, and differ from classic serum sickness in that there is infrequently associated lymphadenopathy and proteinuria, no circulating immune complexes, and no evidence to date of sequelae of the reaction. While further investigation is ongoing, **serum-sickness-like** reactions appear to be due to hypersensitivity and more often occur during or following a second (or subsequent) course of therapy with Ceclor. Such reactions have been reported more frequently in children than in adults with an overall occurrence ranging from 1 in 200 (0.5%) in one focused trial to 2 in 8,346 (0.024%) in overall clinical trials (with an incidence in children in clinical trials of 0.055%) to 1 in 38,000 (0.003%) in spontaneous event reports. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy; occasionally these reactions have resulted in hospitalization, usually of short duration (median hospitalization = two to three days, based on postmarketing surveillance studies). In those requiring hospitalization, the symptoms have ranged from mild to severe at the time of admission with more of the severe reactions occurring in children. Antihistamines and glucocorticoids appear to enhance resolution of the signs and symptoms. No serious sequelae have been reported.
• Stevens-Johnson syndrome, toxic epidermal necrolysis, and anaphylaxis have been reported rarely. Anaphylaxis may be more common in patients with a history of penicillin allergy.
• Gastrointestinal (mostly diarrhea): 2.5%
• Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment.
• As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.
• Rarely, reversible hyperactivity, nervousness, insomnia, confusion, hypertonia, dizziness, and somnolence have been reported.
• Other: eosinophilia, 2%; genital pruritus or vaginitis, less than 1% and, rarely, thrombocytopenia and reversible interstitial nephritis.

Abnormalities in laboratory results of uncertain etiology.
• Slight elevations in hepatic enzymes.
• Transient lymphocytosis, leukopenia, and, rarely, hemolytic anemia and reversible neutropenia.
• Rare reports of increased prothrombin time with or without clinical bleeding in patients receiving Ceclor and Coumadin concomitantly.
• Abnormal urinalysis; elevations in BUN or serum creatinine.
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• False-positive tests for urinary glucose with Benedict's or Fehling's solution and Clinitest® tablets but not with Tes-Tape® (glucose enzymatic test strip, Lilly).

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CONTINUING MEDICAL EDUCATION

(Continued from Page 612)

February 11-15—**Occupational and Environmental Medicine: Session III.** UCSF at Cathedral Hill Hotel, San Francisco. Mon-Fri. 40 hrs. $600. Contact: UCSF.

March 13-17—**Mountain Medicine: '91.** American College of Emergency Physicians at Squaw Valley. Wed-Sun. 22 hrs. $395. Contact: Howard Donner, MD, PO Box 321, Yreka 96097. (800) 888-5632.

OPHTHALMOLOGY

December 13-14—**New Ideas on Common Retinal Disorders.** UCSF at Grand Hyatt Union Square, San Francisco. Thurs-Fri. 12 hrs. $300. Contact: UCSF.

January 13-16—**Contact Lens Association of Ophthalmologists 1991 Annual Meeting.** CLAO at Caesars Palace, Las Vegas, Nevada. Sun-Wed. Contact: CLAO, 523 Decatur St, Ste One, New Orleans, LA 70130-1027. (504) 581-4000.

February 3-7—**10th Annual Squaw Valley Retina Symposium.** Alta-California Ophthalmological Society at Squaw Valley Inn, Olympic Valley. Sun-Thurs. 16 hrs. Contact: Mercy General Hospital, Community Relations, 4001 "J" St, Sacramento 95819. (916) 454-4410.

February 8-10—**60th Midwinter Clinical Conference.** Research Study Club of Los Angeles at Moseley/Salvatori Conference Center, Los Angeles. Fri-Sun. Contact: Research Study Club, PO Box 1216, Murrieta 92362. (714) 677-4482.

March 23—**Pearls of Ocular Therapy.** Scripps Clinic and Research Foundation at La Jolla. Sat. 8 hrs. $120. Contact: Laurie Jones, Box 400S, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-9592.

OTOLARYNGOLOGY

February 8-10—**60th Midwinter Clinical Conference.** Research Study Club of Los Angeles at Moseley/Salvatori Conference Center. Fri-Sun. Contact: Research Study Club, PO Box 1216, Murrieta 92362. (714) 677-4482.

January 18-20—**Triological Society Western Section.** Triological Society at Santa Barbara Biltmore Hotel. Fri-Sun. Contact: David Hilding, MD, Ste 1, Hospital Dr, Price, UT 84501. (801) 637-4327.

PATHOLOGY

February 1-2—**9th Annual Infectious Disease Update.** UCD at Hilton Inn, Sacramento. Fri-Sat. 11 hrs. $175. Contact: UCD.

February 13-15—**Clinical Laboratory Molecular Analysis.** Scripps Clinic and Research Foundation at Hyatt Regency Hotel, La Jolla. Wed-Fri. 21 hrs. $375. Contact: Laurie Jones, Box 400S, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-9592.

April 6—**6th Annual Conference: New Treatments in Chronic Liver Disease.** Scripps Clinic and Research Foundation at Amphitheater of Green Hospital, La Jolla. Sat. 7 hrs. $125. Contact: Laurie Jones, Box 400S, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-9592.

April 17-19—**12th Annual Advances in Infectious Diseases.** UCSF at Sheraton Palace Hotel, San Francisco. Wed-Fri. 18 hrs. $395. Contact: UCSF.

PEDIATRICS

January 23-26—**Health Science Response to Child Maltreatment 1991.** Children's Hospital San Diego at U S Grant Hotel, San Diego. Wed-Sat. 22 hrs. Contact: Children's Hospital, (619) 576-5814.

February 8-10—**Current Concepts in Pediatric Medicine 1991.** Children's Hospital San Diego at Hyatt Islandia Hotel, San Diego. Fri-Sun. 18 hrs. Contact: CME Dept. Children's Hospital, (619) 576-4072.

February 13-15—**16th Annual Symposium on Care of the Sick Newborn.** Memorial UCI Center for Health Education at Hyatt Regency Hotel, Long Beach. Wed-Fri. Contact: UCI.

February 18-20—**Pediatrics Update: 1991.** San Diego State University at Hyatt Islandia, San Diego. Mon-Wed. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

(Continued on Page 682)

DYAZIDE®
25 mg Hydrochlorothiazide/50 mg Triamterene/SKF

Before prescribing, see complete prescribing information in SK&F LAB CO. literature or PDR. The following is a brief summary.

Indications and Usage: *Hypertension or edema in patients who develop hypokalemia on hydrochlorothiazide alone; in patients who require a thiazide diuretic and in whom the development of hypokalemia cannot be risked.*

This fixed combination drug is not indicated for the initial therapy of edema or hypertension except in individuals in whom the development of hypokalemia cannot be risked.

Dyazide may be used alone or as an adjunct to other antihypertensive drugs; dosage adjustments may be necessary.

Contraindications *Concomitant use with other potassium-sparing agents such as spironolactone or amiloride; potassium supplements (except in presence of severe hypokalemia); anuria, acute and chronic renal insufficiencies or significant renal impairment; hypersensitivity to drug or other sulfonamide-derived drugs; preexisting elevated serum potassium concentration.*

Warnings *Abnormal elevation of serum potassium levels (greater than or equal to 5.5 mEq/liter) can occur with all potassium-conserving diuretic combinations, including Dyazide. Hyperkalemia is more likely to occur in patients with renal impairment and diabetes (even without evidence of renal impairment), and in the elderly or severely ill. Since uncorrected hyperkalemia may be fatal, serum potassium levels must be monitored at frequent intervals especially in patients first receiving Dyazide, when dosages are changed or with any illness that may influence renal function.*

If hyperkalemia is suspected, obtain an ECG and monitor serum potassium. If hyperkalemia develops, discontinue Dyazide and initiate thiazide therapy if needed. Persistent hyperkalemia may require dialysis. Monitor serum electrolytes frequently in patients with mild renal dysfunction and in diabetic patients. In patients who may develop respiratory or metabolic acidosis, monitor serum electrolytes and acid/base balance frequently.

Precautions *The bioavailability of the hydrochlorothiazide and triamterene components of Dyazide is about 50% of the maximum obtainable with oral therapy. Theoretically, a patient transferred from therapy with hydrochlorothiazide with or without triamterene might show an increase in blood pressure, fluid retention, or change in serum potassium. Extensive clinical experience with Dyazide, however, suggests that these conditions have not been commonly observed in clinical practice. (See CLINICAL PHARMACOLOGY.) Use thiazides cautiously in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease; potassium depletion induced by the thiazide may be important in this connection, administer Dyazide cautiously and be alert for such early signs of impending coma as confusion, drowsiness and tremor, if mental confusion increases, discontinue Dyazide for a few days; attention must be given to other factors that may precipitate hepatic coma, such as blood in the gastrointestinal tract or preexisting potassium depletion. If patients develop hypokalemia, which is uncommon with Dyazide, increase potassium intake (i.e., with supplements or potassium-rich foods). If repeat determinations show serum potassium concentrations below 3.0 mEq/L, discontinue Dyazide and initiate potassium chloride supplementation. Institute corrective measures cautiously and monitor serum potassium concentrations frequently, especially in patients receiving digitalis or those with a history of cardiac arrhythmias. Diuretics may aggravate existing electrolyte imbalances, especially at high dosages or in patients on salt-restricted diets. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Chloride replacement may be required in the treatment of metabolic acidosis. If dilutional hyponatremia develops, restrict water intake. In actual salt depletion, initiate sodium chloride replacement. Use Dyazide cautiously in patients with a history of renal stone formation.*

If hyperkalemia develops when treating for hypokalemia, take corrective measures. Also discontinue Dyazide and, if appropriate, substitute a thiazide diuretic until potassium levels return to normal. Do periodic BUN and serum creatinine determinations, especially in the elderly and in patients with suspected or confirmed renal insufficiency. Serum PBI levels may decrease without signs of thyroid disturbance. Discontinue thiazides before conducting parathyroid function tests.

Angiotensin-converting enzyme (ACE) inhibitors can elevate serum potassium, use with caution with Dyazide. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. A few occurrences of acute renal failure have been reported in patients on Dyazide when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with Dyazide. Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine, therefore use cautiously in patients undergoing surgery. Monitor electrolytes in patients taking amphotericin B, corticosteroids or corticotropin concomitantly. Thiazides may potentiate the action of other antihypertensive drugs. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be needed. Dyazide may raise the level of blood uric acid; dosage adjustments of antigout medication may be needed to control hyperuricemia and gout. The following agents given with triamterene may promote serum potassium accumulation and possibly result in hyperkalemia, especially in patients with renal insufficiency: blood from blood bank (may contain up to 30 mEq of potassium per liter of plasma or up to 65 mEq of potassium per liter of whole blood when stored for more than 10 days); low-salt milk (may contain up to 60 mEq of potassium per liter); potassium-containing medications (such as parenteral penicillin G potassium), and salt substitutes (most contain substantial amounts of potassium). Exchange resins, such as sodium polystyrene sulfonate, whether administered orally or rectally, reduce serum potassium concentrations by sodium replacement of the potassium, fluid retention may occur in some patients because of the increased sodium intake. Chronic or overuse of laxatives may reduce serum potassium concentrations by promoting excessive potassium loss from the intestinal tract. laxatives may interfere with the potassium-retaining effects of triamterene. The effectiveness of methenamine may be decreased when used concurrently with hydrochlorothiazide because of alkalinization of the urine. Dyazide will interfere with the fluorescent measurement of quinidine.

There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy only if clearly needed. Thiazides and triamterene cross the placental barrier and appear in cord blood. The use of thiazides in pregnancy requires weighing the anticipated benefit against possible hazards, including fetal or neonatal jaundice, pancreatitis, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. Thiazides appear, and triamterene may appear, in breast milk. If use of the drug is essential, the patient should stop nursing. Safety and effectiveness in children have not been established.

Adverse Reactions *The serious adverse effects associated with Dyazide have commonly occurred in less than 0.1% of patients treated with this product. Anaphylaxis, rash, urticaria, photosensitivity, cardiac arrhythmias, postural hypotension, diabetes mellitus, hyperkalemia, hyperglycemia, glycosuria, hyperuricemia, hypokalemia, hyponatremia, acidosis, hypochloremia, jaundice and/or liver enzyme abnormalities, pancreatitis, nausea and vomiting, diarrhea, constipation, abdominal pain, acute renal failure, interstitial nephritis, renal stones composed primarily of triamterene, elevated BUN and serum creatinine, abnormal urinary sediment, leukopenia, thrombocytopenia and purpura, megaloblastic anemia, muscle cramps, weakness, fatigue, dizziness, headache, dry mouth, impotence, sialadenitis. Thiazides alone have been shown to cause the following additional adverse reactions: paresthesias, vertigo, xanthopsia, transient blurred vision, allergic pneumonitis, pulmonary edema, respiratory distress, necrotizing vasculitis, exacerbation of lupus, aplastic anemia, agranulocytosis, hemolytic anemia. In neonates and infants: thrombocytopenia and pancreatitis—rarely, in newborns whose mothers have received thiazides during pregnancy.*

Supplied: *Capsules containing 25 mg hydrochlorothiazide and 50 mg triamterene, in bottles of 1000 capsules, in Single Unit Packages (unit-dose) of 100 (intended for institutional use only), in Patient-Pak™ unit-of-use bottles of 100.*

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Articles

Subacute Poisoning With Phosalone, an Organophosphate Insecticide

MICHAEL A. O'MALLEY, MD, MPH, *Sacramento, and* STEPHEN A. McCURDY, MD, MPH, *Davis, California*

An illness characterized by weakness, dizziness, and gastrointestinal symptoms was identified among a crew of 30 migrant field-workers employed by a grape grower in Madera County, California, during August 1987. The onset of symptoms occurred between August 24 and August 30 and a median of 9 days from the date of first employment. The first crew member sought medical treatment on August 26, and 10 crew members were admitted to hospital between August 27 and August 30. For most workers, gastrointestinal and constitutional symptoms resolved shortly after admission, but 4 patients had episodes of severe sinus bradycardia persisting for several days. On the day of admission, transient atrioventricular dissociation developed in 2 persons. Interviews with 16 crew members not admitted to the hospital identified only 1 additional worker ill with gastrointestinal symptoms, but all 16 had moderate to severe inhibition of both plasma and red blood cell cholinesterase. Four other workers who were tested but not interviewed also had cholinesterase depression. The crew had had exposure since August 19 to the organophosphate insecticide phosalone, which was last applied to the vineyard on July 21, or 29 days earlier. Although this is the first report unequivocally linking phosalone to field-worker poisoning, the delayed onset and nonspecific nature of the symptoms associated with subacute poisoning may have hindered the recognition of previous similar episodes.

(O'Malley MA, McCurdy SA: Subacute poisoning with phosalone, an organophosphate insecticide. West J Med 1990 Dec; 153:619-624)

Organophosphate pesticides are widely used in modern agriculture. In 1987 the California Department of Food and Agriculture (CDFA) reported more than 15 million lb was sold throughout California.[1] These compounds inhibit acetylcholinesterase, leading to overactivity of portions of the central nervous system dependent on acetylcholine-mediated neurotransmission. In humans with exposure to toxic amounts of organophosphate pesticides, symptoms of acute poisoning commonly include salivation, lacrimation, urination, diarrhea, vomiting, bradycardia, and peripheral weakness or paralysis.[2] When poisoning is severe, central nervous system effects such as seizures and coma may also occur and may culminate in death. Symptoms of organophosphate toxicity are nonspecific, and the diagnosis requires a high degree of clinical suspicion.

In recent years outbreaks of organophosphate poisoning in California field-workers have frequently involved large groups presenting to the emergency department of a rural hospital for evaluation of acute gastrointestinal symptoms after a single accidental overexposure to a highly toxic organophosphate insecticide.[3] In this context, group and individual cholinesterase data may be difficult to interpret, but the common exposure history and epidemic nature of the illness facilitate diagnosis.[4] In cases of accidental or deliberate ingestion of organophosphates, diagnosis is facilitated by the recent history of ingestion. There is typically an interval of less than 24 hours between the exposure and the start of symptoms.[5]

Individual cases of field-worker poisoning may prove difficult to identify without a recognized outbreak of illness. As illustrated by the series we report here, recognition may be especially difficult when the gradual absorption of a moderately toxic organophosphate leads to a subacute onset of symptoms. Although fully apparent illness may eventually develop in a small number of cases, some persons may be asymptomatic or may have mild and nonspecific symptoms despite marked cholinesterase inhibition. The clinical syndrome of subacute intoxication shown by the most severely affected patients may differ from that seen in acute poisonings, as illustrated in our series by the occurrence of atrioventricular dissociation and severe bradycardia without excess respiratory and gastrointestinal tract secretions typical of acute cholinergic crisis.

Patients and Methods

California law requires physicians to report confirmed and suspected cases of pesticide poisoning to the appropriate county health officer. These reports are then forwarded to the county agricultural commissioner's office for investigation of the circumstances of pesticide exposure. Authorities in the California Department of Health Services and the CDFA are also notified. Work-related cases may also enter into the reporting network on a physician's filing of a Workers' Compensation report with the state Department of Industrial Relations.[6]

Our series involves an incident of poisoning by the insecticide phosalone (S-[(6-chloro-2-oxo-3[2H]-benzoxazolyl) methyl] O,O-diethylphorodithioate) that was reported to the CDFA during August (and September) of 1987. The investigation of these cases involved interviewing affected and unaffected employees by officials from the state and county agricultural departments; reviewing grower application histories; sampling implicated fields for pesticide residues; and examining in detail medical records for all exposed persons who sought medical treatment.

The suppression of cholinesterase activity was quantita-

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ABBREVIATIONS USED IN TEXT

CDFA = California Department of Food and Agriculture
LD_{50} = minimum lethal dose

tively estimated from the midpoint of the normal range, using the method of Namba and co-workers.[5] The relationship between cholinesterase depression and several postulated exposure factors was evaluated using the Wilcoxon rank sum test for independent samples.[7] Factors evaluated included work history, sources of food, place of residence, the use of irrigation water for washing clothes or bathing, and the presence of symptoms. Information on work history and sources of food and water was obtained exclusively from interviews. Where a direct interview was not possible, addresses and information regarding the presence or absence of symptoms were obtained from medical records. All chemical residue measurements were carried out by Chemical Laboratory Services at CDFA, including dislodgeable foliar residue samples for phosalone and multiresidue screens for carbamates and other organophosphates.

Results

Report of Cases

On August 26, 1987, a 25-year-old man (patient 1) sought treatment at a community hospital in Madera County, California, because of dizziness, disorientation, and vomiting that began while he was harvesting grapes for a Madera grower (grower A) that afternoon. No other members of the 30-man crew were ill. His pulse rate and other vital signs were normal; the findings of a physical examination were unremarkable except for mild epigastric and suprapubic tenderness. A complete blood count and chemistry panel—serum creatinine, potassium, sodium, carbon dioxide, chloride, calcium, and glucose levels—were within normal limits. A diagnosis of acute gastroenteritis was made. After receiving 2.5 liters of 5% dextrose in a solution of 0.25 normal saline, the patient felt better and was discharged.

He returned at 12:40 PM the next day because of persistent weakness and dizziness associated with the occurrence of diarrhea, crampy abdominal pain, lacrimation, and salivation. On reexamination, he appeared weak and his pulse rate was 48 beats per minute; his blood pressure and respiratory rate were normal. His pupils were 3 mm in diameter, the lungs were clear, and the abdomen was nontender. Laboratory examinations again showed a normal complete blood count, chemistry panel, and urinalysis. The plasma cholinesterase level was 304 units per liter (normal, 964 to 2,400); the erythrocyte cholinesterase content was 4,360 units per liter (normal, 9,348 to 16,996). At 2:35 PM he had an episode of severe bradycardia with a supraventricular rhythm of 32 beats per minute (Figure 1, top). His blood pressure was 109/74 mm of mercury, but there was no notation describing symptoms or postural changes in the blood pressure. He received 1 mg of intravenous atropine, and in several minutes his heart rate increased to 60 beats per minute.

On admission to the hospital, the patient was given a second dose of 1 mg of atropine intravenously and was placed on cardiac telemetry. Because of recurrent episodes of moderate bradycardia, he required a total of 4.5 mg of atropine on his first hospital day (Table 1). Severe bradycardia recurred at 5:00 AM on the second hospital day (heart rate, 37 beats per minute) and again at 7:34 AM, with an initial sinus pause of 2.6 seconds, followed by recovery to an estimated heart rate of 39 beats per minute (Figure 1, bottom). After a dose of atropine, his heart rate increased to 75 beats per minute. During the next several days, the patient received frequent doses of atropine for episodes of moderate sinus bradycardia. Except for an intermittent headache, nausea, and a single episode of loose stool reported on the seventh hospital day, he was asymptomatic and his lungs remained clear to auscultation. He was asymptomatic on discharge but had persistent mild bradycardia. A total of 16.5 mg of atropine was administered throughout his eight-day hospital stay (Table 1).

Although other crew members were asymptomatic when patient 1 first reported symptoms, on August 29, a 15-year-old boy (patient 2) collapsed at the same labor camp shortly after work. He was taken by an acquaintance to the community hospital along with two other members of the crew (patients 3 and 4). All three had nausea and abdominal cramping and were later admitted. Cholinesterase values were well below the lower limit of normal (Table 1). On instructions from the emergency department staff, the acquaintance returned to the labor camp to see if any additional camp residents were ill. As a result, patients 5 through 10 were admitted to the hospital late in the evening of August 29 or early in the morning of August 30 with symptoms as shown in Table 1.

Patients 3, 5, and 6 each had severe bradycardia comparable to that of the index case. Aside from postural dizziness suffered by patient 5 on the third hospital day, none were symptomatic when these episodes occurred. Patient 6 also had episodes of atrioventricular dissociation at 6:34 AM and 5:43 PM on the first day in the hospital (Figure 2, top and bottom). Hospital records showed that the workers were asymptomatic when discharged (between September 3 and September 5), but many still had a mild sinus bradycardia (between 50 and 60 beats per minute).

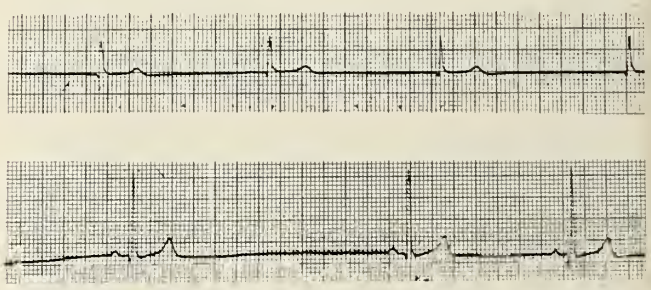

Figure 1.—Cardiac telemetry strips taken on patient 1 show episodes of severe bradycardia: **Top**, On first hospital day at 2:35 PM, patient had a supraventricular rhythm of 32 beats per minute. **Bottom**, On second hospital day at 7:34 AM, there was a 2.6-s sinus pause followed by recovery to about 39 beats per minute.

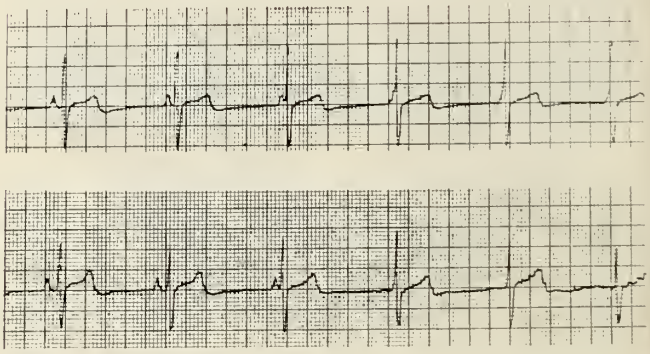

Figure 2.—Cardiac telemetry strips taken on patient 6 on first hospital day show episodes of atrioventricular dissociation at **(top)** 6:46 AM and **(bottom)** 5:43 PM.

TABLE 1.—*Summary of Clinical Course of 10 Patients Admitted to Hospital With Subacute Phosolone Poisoning*

Patient	Age, yr	Date	Symptoms	Cholinesterase Level,* U/liter		Lowest Heart Rate, bpm	Atropine, mg	Pralidoxime, grams	Telemetry Findings
				Plasma	RBC				
1	25	8/27	Vomiting, diarrhea, dizziness, disorientation, lacrimation, salivation, abdominal cramps	304	4,360	32	4.5	None	SB
		8/28	Headache, nausea	362	4,680	30	5.0	...	SB
		8/29	None	545	5,080	44	2.0	...	SB
		8/30	Headache	609	6,200	40	1.0	...	SB
		8/31	None	724	5,280	46	3.0	...	SB
		9/1	Headache, nausea	864	5,720	46	1.0	...	SB
		9/2	Loose stool, abdominal cramps	1,084	6,020	50 to 60	...	...	SB
		9/3	Discharged	...	...	...	...	...	
2	15	8/29	Dizziness, nausea, abdominal cramps, vomiting	326	4,920	68	...	None	None
		8/30	None	...	...	72	...	...	
		8/31	Discharged	...	...	48	...	...	
3	24	8/29	Dizziness, nausea, abdominal cramps, vomiting	244	3,200	56	0.6	...	SB
		8/30	None	...	...	45	...	1	SB
		8/31	None	454	4,800	43	...	1	SB
		9/1	None	560	4,120	37	0.5	1	SB
		9/2	Discharged	...	...	44	...	...	SB
4	23	8/29	Weakness, nausea, abdominal pain, dizziness	346	4,680	60	None	None	None
		8/30	None	...	...	72	...	...	
		8/31	Headache	...	...	54	...	...	
5	44	8/30	Weakness, dizziness	260	3,760	38	4.0	1	SB
		8/31	None	394	5,400	42	0.5	...	SB
		9/1	Dizziness on rising	557	6,440	36 to 38	2.0	...	SB
		9/2	None	810	7,800	39	1.5	...	SB
		9/3	None	782	6,320	39	0.5	...	SB
		9/4	None	864	7,440	48	...	...	SB
		9/5	Discharged	...	...	...	...	...	None
6	19	8/30	Weakness	501	5,160	39	3.5	1	SB, AV dissociation
		8/31	None	644	6,760	38	2.5	...	SB
		9/1	None	821	7,240	34	1.0	...	SB
		9/2	None	968	8,040	53	...	...	SB
		9/3	None	924	7,240	34	1.5	...	SB
		9/4	Chest pain, headache	951	12,800	52	...	...	SB
		9/5	Discharged	...	...	...	...	...	
7	59	8/30	Weakness	238	3,880	50 to 55	0.5	1	SB
		8/30	None	303	6,160	...	...	...	
		8/31	None	385	6,080	48	...	...	SB
		9/1	None	582	6,200	72	...	...	None
		9/2	None	760	7,960	52	...	...	None
		9/3	None	834	8,280	NR	...	...	None
8	54	8/29	Nausea, headache, abdominal pain, dizziness	270	4,000	60	...	1	SB
		8/30	None	346	4,240	58	...	...	SB
		8/31	Headache	435	7,000	61	...	...	SB
		9/1	None	664	8,280	46	1.0	...	SB
		9/2	None	805	6,820	50	...	...	
		9/3	None	793	6,760	54	...	...	
9	18	8/29	Nausea, vomiting, dizziness, abdominal tenderness	330	4,920	60	...	None	None
		8/30	None reported	360	5,520	58	...	1	SB
		8/31	None reported	474	7,560	53	...	...	SB
		9/1	None reported	678	8,360	52	...	...	SB
		9/2	None reported	844	7,800	...	...	...	None
		9/3	Discharged	...	...	...	...	...	
10	49	8/29	Dizziness, salivation, headache	320	3,680	56	None	1	SB
		8/30	None reported	382	4,480	56	...	...	SB
		8/31	None reported	537	9,400	60	...	...	SR
		9/1	None reported	737	8,400	64	...	...	None
		9/2	None reported	960	6,360	>50	...	...	
		9/3	Discharged	930	11,040	...	...	...	

AV = atrioventricular, NR = not recorded, RBC = erythrocyte, SB = sinus bradycardia, SR = sinus rhythm

*Cholinesterase tests done using modified Ellman (colorimetric) method. Normal range: RBC cholinesterase, 9,348 to 16,996 (midpoint is 13,172); plasma cholinesterase, 964 to 2,400 (midpoint is 1,682).

Except for bradycardia, there were few signs of cholinergic crisis among the 10 patients during their hospital stays. Although patient 3 had chest tightness on admission, he never showed respiratory distress, and his lungs remained clear to auscultation.

On August 31 and September 1, the remaining members of the harvesting crew had cholinesterase tests, and all but four were available for interview on September 2. These interviews revealed an unreported case of gastrointestinal symptoms in a crew member (patient 27) whose date of symptom occurrence corresponded to the dates reported by the 10 patients previously admitted to the hospital (Figure 3). Crew member 28 reported atypical symptoms that did not begin until September 6; this member was counted as asymptomatic in the subsequent analysis.

Results of the cholinesterase tests showed that all crew members had enzyme activity levels depressed far below the predicted values (Table 2). For the crew as a whole, the median degree of plasma cholinesterase inhibition was 64.9%; for erythrocyte cholinesterase, the median degree of inhibition was 52.5%. The degree of cholinesterase inhibition was not influenced by previous work done during the 1987 harvest season or by the consumption of grapes at home or at work (Table 3). It was noted that the 11 symptomatic workers had a significantly greater degree of cholinesterase inhibition than did the 15 who were asymptomatic (Figure 4). Although the use of the irrigation canal for washing clothes or bathing was suspected as a possible source of exposure, it proved to have a significant negative relationship with the occurrence of cholinesterase depression. Crew members who did not live at the camp may have

TABLE 2.—*Cholinesterose Volues for Crew Members With Subocute Phosalone Poisoning Not Admitted to Hospitol**

	Plasma Cholinesterase		RBC Cholinesterase		
Crew Member	Measured Value	% Below Midpoint of Normal Range	Measured Value	% Below Midpoint of Normal Range	Symptoms
11	788	53.2	4,800	63.6	None
12	690	59.0	7,680	41.7	†
13	608	63.9	6,760	48.7	None
14	809	51.9	6,440	51.1	None
15	695	58.7	6,520	50.5	†
16	638	62.1	6,520	50.5	None
17	749	55.5	7,000	46.9	None
18	562	66.6	6,520	50.5	None
19	573	65.9	8,600	34.7	None
20	1,167	30.6	6,440	51.1	†
21	1,035	38.5	6,520	50.5	†
22	868	48.4	5,160	60.8	None
23	674	59.9	6,080	53.8	None
24	1,108	34.1	8,360	36.5	None
25	769	54.3	6,760	48.7	None
26	939	44.2	6,640	49.6	None
27	0.26	74.8	0.37	58.9	Indigestion, stomach pains, vomiting, nausea, tingling of body
28	0.18	82.5	0.26	71.1	Numbness in tongue
29	0.31	69.9	0.49	45.6	None
30	0.20	80.6	0.40	55.6	None

RBC = erythrocyte

*Cholinesterase tests for crew members 27 through 30 were done using the Michel method at a referral laboratory in Fresno, California. Normal range in δ pH units: RBC cholinesterase, 0.55 to 1.25 (midpoint is 0.90); plasma cholinesterase, 0.41 to 1.65 (midpoint is 1.03). Other tests were carried out using the Ellman method at the hospital laboratory. Normal range in units per liter: RBC cholinesterase, 9,348 to 16,996 (midpoint is 13,172); plasma cholinesterase, 964 to 2,400 (midpoint is 1,682).

†Crew member was not available for interview.

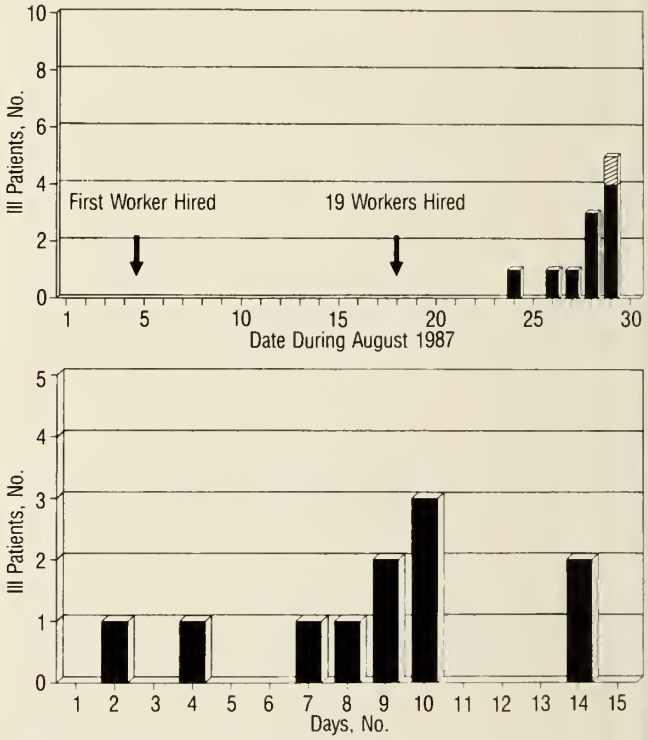

Figure 3.—The graphs show the distribution of cases by time of occurrence: **Top**, Cases are shown by date of onset; **bottom**, cases are shown by latency between first exposure and start of symptoms. ■ = patient admitted to hospital, ▨ = patient not admitted

TABLE 3.—*Investigotion of Foctors Postulated to Affect Cholinesterose Depression*

Factor	Number Exposed	Estimated % Inhibition Median Value		Number Unexposed	Estimated % Inhibition Median Value			
		RBC	Plasma		RBC	P Value*	Plasma	P Value*
Labor camp residence	19	61	70	7	51	.236	61	.112
Prior work, Mexico	8	52	68	16	60	.540	72	.760
Prior work, Oregon	10	56	64	14	57	.770	78	.219
Bathing or washing in irrigation canal	12	49	63	10	69	.001	81	.003
Ate grapes at work	16	57	72	8	59	.783	64	.951
Ate grapes at home	6	50	67	18	62	.155	72	.640
Food provided by crew supervisor	13	67	80	6	57	.254	77	.930
Symptomatic illness	11	68	81	15	51	.002	60	.001

RBC = erythrocyte

*Based on the difference between exposed and unexposed groups in the Wilcoxon rank sum test.

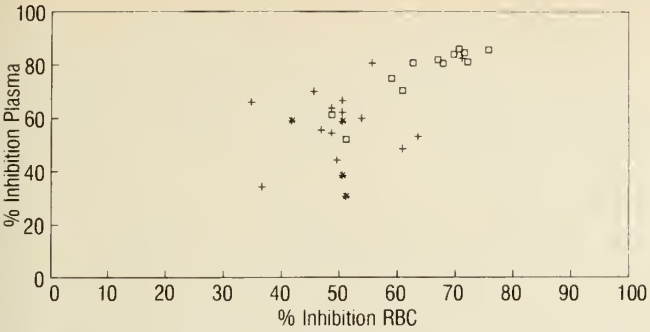

Figure 4.—The percentage of depression for plasma and erythrocyte (RBC) cholinesterase levels is shown in symptomatic and asymptomatic workers. □ = worker with gastroenteritis, + = asymptomatic worker, * = worker not interviewed

had even less adequate facilities. Five crew members (14, 18, 22, 24, and 30) reported that they slept either in their automobiles or in the fields since they began working for the Madera County grape grower and had no temporary residence during their stay in Madera.

Work History and Pesticide Residue Data

On investigation of these illnesses by the Madera County Agricultural Commissioner's Office, it was found that before mid-August, crew members had no common exposure history. Several persons reported having worked previously in Oregon, others in Idaho, and still others in southern Santa Clara County and the San Joaquin Valley of California. Dates of employment in Madera County ranged from August 5 to August 26, but most crew members began work for grower A on August 19, manually harvesting a block of French Colombard grapes. This block had been treated May 13 with 25% phosalone wettable powder (7 lb per acre). On July 21 various rows in this block received a second application of phosalone emulsifiable concentrate at 5 pt per acre and phosalone wettable powder at 3 lb per acre. The seven-day interval to allow safe reentry into phosalone-treated fields[8] elapsed on July 28, one week before the first worker entered the field (Figure 3).

Other blocks worked between August 19 and August 26 included 35 rows of Thompson seedless grapes treated with 25% phosalone wettable powder at 7 lb per acre on May 15. According to the grower's application records, all blocks within the vineyard had received at least one treatment with phosalone, during either May or July, and no other cholinesterase-inhibiting insecticides were applied during the 1987 growing season. This was confirmed by chemical analysis of field samples showing persistence of phosalone (13 dislodgeable foliar residue samples with levels ranging from 0.3 to 2.0 μg per cm^2; median value, 1.3 μg per cm^2) and its toxic transformation product, phosalone-oxon (ranging from nondetectable to 0.29 μg per cm^2; median value, 0.12 μg per cm^2). All samples were thus below the 7.0 μg per cm^2 dislodgeable foliar residue estimated as a safe level for preventing cholinesterase inhibition and acute poisoning in field-workers.[9] In none of the 13 samples taken was residue of any other cholinesterase-inhibiting insecticide found.

Discussion

This series of poisonings associated with the insecticide phosalone underlines the unpredictable relationship between cholinesterase inhibition and the occurrence of related symptoms. Although there was a significant statistical relationship between symptoms and cholinesterase depression in the crew as a whole, some workers with greater than 80% depression of plasma cholinesterase levels remained asymptomatic. The absence of symptoms in most crew members is likewise unexpected when cholinesterase data from the current outbreak are compared with previous case series involving the acute onset of organophosphate poisoning.[3-5] This finding strongly suggests that both the rate and the magnitude of cholinesterase depression are important determinants of symptomatic illness after exposure to organophosphate insecticides.

The principal clinical features of interest in this series were the atrioventricular dissociation and severe sinus bradycardia among the patients admitted to the hospital. Atrioventricular dissociation and bradycardia were unexpected because cardiac side effects of organophosphate exposure have usually been associated with an acute overdose of the agent, accompanied by florid signs of cholinergic overstimulation.[10-12] Although the bradycardia was well tolerated during bed rest or relative inactivity, six of the ten patients receiving hospital care initially presented with symptoms of dizziness or syncope, and one patient (patient 5) had transient postural dizziness on his third day in the hospital. These symptoms may have been due to direct pharmacologic effects of acetylcholine on the central nervous system, but they could also plausibly be explained by the severe bradycardia shown by four of the eight patients monitored with cardiac telemetry. Because few cases of acute phosalone intoxication have previously been published, it is impossible to ascertain whether the prominent cardiac effects seen in these persons were attributable primarily to the slow onset of poisoning or were a unique feature of illness after exposure to phosalone.

The outbreak reported here is the first instance in which phosalone has been identified as the principal agent responsible for a mass field-worker poisoning incident. Although it has previously been implicated in conjunction with other organophosphate pesticides, phosalone's moderate toxicity (for rats, minimum oral lethal dose [LD_{50}] is 120 mg per kg and the dermal LD_{50} is 1,530 mg per kg[13]) made it seem a less likely cause of those outbreaks than were other, more toxic compounds.[14-16] The finding of dislodgeable residue levels below the estimated safe level[9] of 7.0 μg per cm^2 also militated against phosalone's being a contributing cause in each of the previous episodes. An investigation of the episode reported here, however, shows that illness may occur at residue levels well below 7.0 μg per cm^2. After the investigation of this outbreak, two similar phosalone-related outbreaks of illness—also accompanied by cases of asymptomatic cholinesterase depression—were reported at the beginning of September 1987.[17] Emergency restrictions on harvesting phosalone-treated vineyards were then imposed for the remainder of the harvest season (September, October, and November of 1987).

A principal distinction between phosalone and other organophosphate insecticides is its environmental persistence. General surveys of hand-harvest operations in California, involving samples collected by CDFA between 1975 and 1984, have shown that harvester exposure to organophosphate residues is intermittent, with only 6% of the 2,088 fields sampled in this series having detectable residue levels.[18] Phosalone, by contrast, typically persists well beyond its seven-day reentry period, and in California's Central Valley, its environmental half-life ranges as long as 30 days.[19-23] Given the recognition of illness in field-workers associated with phosalone levels of 0.3 to 2.9 μg per cm^2 dislodgeable foliar residue (following applications made more than a month earlier), adjustment of the reentry inter-

val was deemed an impractical method of regulating this compound, except for use on machine-harvested crops. By agreement between CDFA and the manufacturer, phosalone use in California was therefore eliminated for all manually harvested crops beginning in 1988.

Conclusion

To treating physicians, a physiologic adaptation to cholinesterase inhibition seen in subacute organophosphate poisoning presents many clinical dilemmas. Should patients presenting with only mild sinus bradycardia be admitted to the hospital, and should all these patients be monitored routinely with cardiac telemetry? Does moderate to severe bradycardia with no other symptoms of cholinesterase inhibition warrant the aggressive use of atropine recommended for serious acute poisonings?[24] Should the use of pralidoxime be recommended despite the expectation of only a partial recovery of cholinesterase activity? Although it is evident that a careful observation of patients for episodes of severe bradycardia is warranted, the other questions cannot be answered with certainty and deserve careful consideration in each case of organophosphate poisoning.

Clinicians must recognize that some incidents of poisoning among agricultural workers may represent "sentinel health events."[25] As we have shown here, it is appropriate to seek an evaluation of co-workers when it has been determined that one field-worker or a small group has been poisoned. Given a lengthy and variable delay between the exposure and the occurrence of symptoms, persons with subacute poisoning are more likely to present for medical evaluation singly or in small groups. Many patients with no or mild symptoms may therefore escape medical attention. Although less likely to present as illness clusters, pesticide applicators who handle organophosphates may also be at risk for subacute poisoning. Physicians' awareness of the spectrum of pesticide illness among field-workers is essential for the recognition, treatment, and prevention of poisoning with cholinesterase-inhibiting insecticides.

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Methamphetamine
Stimulant of the 1990s?

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During the past several years, the use of a smokable form of methamphetamine hydrochloride called "ice" has increased rapidly. The heaviest use has occurred on the West Coast and in Hawaii. Many regional emergency departments treat more methamphetamine users than cocaine-intoxicated patients. The ease of synthesis from inexpensive and readily available chemicals makes possible the rampant abuse of a dangerous drug that can produce a euphoria similar to that induced by cocaine. Clinicians should be familiar with the medical effects and treatment of acute methamphetamine toxicity.

(Derlet RW, Heischober B: Methamphetamine—Stimulant of the 1990s? West J Med 1990 Dec; 153:625-628)

A dramatic increase has occurred in the illicit production and use of methamphetamine hydrochloride (HCl) over the past several years (M. Glover, "State Production of Speed Worries U.S. Drug Officials," *Sacramento Bee,* October 10, 1988, p1).[1-3] Endemic areas for this increase include the Pacific Coast states and Hawaii.[4] In 1987 in San Diego County, California, methamphetamine intoxication played a role in 40% of all drug-related homicides.[5] This represents a 52% increase in methamphetamine involvement in serious crime over the previous year. In San Bernardino County, California, the number of coroners' cases involving methamphetamine use has been twice that of cocaine.[6] At present, this epidemic appears confined to the West Coast where in some emergency departments, the number of visits resulting from methamphetamine intoxication exceeds that necessitated by cocaine use.[6,7] Although data from the National Institute on Drug Abuse indicate that cocaine abuse is still greater than that of methamphetamine, the new trend is of great concern.[8]

Methamphetamine provides a euphoria similar to that of cocaine.[9] Studies in animals have shown that methamphetamine and cocaine induce similar behavior.[10] The smokable form of methamphetamine ("ice") can bring on an immediate euphoria with effects that may last many times longer than those of cocaine.[4] Methamphetamine abuse involves a wide age range, and epidemic methamphetamine abuse has recently been described in adolescents. In one inpatient adolescent drug treatment unit, methamphetamine was listed as the drug of choice by about 80% of patients recently admitted.[1] The reasons given for this preference include availability, low cost, and a longer duration of action compared with cocaine. Both oral and intravenous use are well documented, but the use of smokable methamphetamine has received little attention in medical literature.

History

Amphetamine was introduced in the 1930s in the form of inhalers for treating rhinitis and asthma.[11] The stimulant, euphoriant, and anorectic effects of amphetamine were quickly recognized, leading to its abuse. A report in 1937 stating that amphetamine could enhance intellectual performance through enhanced wakefulness further contributed to amphetamine abuse.[12] Amphetamine was used by some foreign armies during the Second World War, allegedly to increase wakefulness and attention.[13] After the mid-1940s, epidemics of amphetamine abuse occurred in several countries, most notably Japan and Sweden. Initial federal controls were enacted in the late 1950s, but amphetamine continued to be abused by some students, athletes, shift workers, and truck drivers into the next decade.[14] The Controlled Substance Act of 1970 stringently regulated the manufacturing of amphetamine. As a result, the availability of dextroamphetamine sulfate (Dexedrine) and other pharmaceutical amphetamines decreased. Despite the declining availability of pharmaceutically synthesized amphetamines, methamphetamine use has increased notably.

Illicit Production

Unlike D-amphetamine, methamphetamine is easy to synthesize in a crude laboratory.[15] Like other sympathomimetic drugs, both are derivatives of phenylethylamine. Structurally, the substances differ in that a methyl group attaches to the terminal nitrogen of methamphetamine. Although some states have enacted laws decreasing the availability of necessary precursor chemicals,[16] these agents may still be obtainable in neighboring states.

One common method of synthesis begins with L-ephedrine, which is reduced to methamphetamine using hydriodic acid and red phosphorus.[17] Variations on this process include using a different acid or catalyst or a substituted ephedrine such as chloroephedrine or methylephedrine. The product is pure D-methamphetamine, which is several times more active than the L form. The ephedrine reduction process is responsible for more than 90% of the methamphetamine produced in southern California (P. Gregory, Drug Enforcement Administration, Sacramento, California, oral communication, November 1988). The methamphetamine produced is a lipid-soluble pure base form, which is volatile and evaporates if left exposed to room air. The producer, therefore, uses hydrochloride to

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ABBREVIATIONS USED IN TEXT

CNS = central nervous system
HCl = hydrochloride
MDMA = methylenedioxymethamphetamine

convert it to the water-soluble form, methamphetamine-HCl powder. This substance has traditionally been sold on the street as "speed," "crank," "go," "crystal," or methamphetamine, and it is highly water soluble.

Other stimulants such as cocaine, phenylpropanolamine hydrochloride, D-amphetamine, ephedrine, or pseudoephedrine have been mixed with or substituted for methamphetamine. Several years ago, street methamphetamine was highly impure and found in only 40% of the street-purchased drug.[18] More recent information from law enforcement laboratories suggests that the methamphetamine available now is nearly pure.[6] Some clandestine chemists purposely produce other stimulants with toxicity of their own, which may be sold as methamphetamine. These stimulants structurally resemble methamphetamine and include methylenedioxymethamphetamine (MDMA), methylenedioxyamphetamine (MDA), 2,5-dimethoxy-4-methylamphetamine (DOM), and bromodom (DOB) and have been referred to as "designer drugs."[19] The routine toxicologic screen may not detect many of the new congeners, such as MDMA, and the drugs may produce symptoms indistinguishable from those induced by methamphetamine.[20,21] Illicitly synthesized methamphetamine may be contaminated by nonstimulant organic or inorganic substances. Lead poisoning and exposure to carcinogenic material have been reported.[22] Street methamphetamine may be mixed with cocaine, and studies show that 8% to 20% of street-available stimulants contain both drugs.[18] In a recent report on cocaine intoxication, 7% of patients sought medical help because of the concurrent use of cocaine and amphetamines.[23]

Ice

The term "ice" originated in the Far East as the result of synthesizing large crystals of methamphetamine through the ephedrine-reduction method (M. Corwin, "Potent Form of Speed Could Be the Drug of '90s," *Los Angeles Times*, October 8, 1989, p1). Once the methamphetamine HCl is produced, making ice involves a process analogous to making rock candy out of sugar. The methamphetamine HCl is slowly added to water, heated to 80°C to 100°C until a supersaturated solution is obtained, and the slurry is then cooled. The pure HCl salt of methamphetamine, also known as ice, precipitates from this. Isopropanol has been used as the solvent in place of water. The many variations of this process result in an unreliable removal of impurities. Many physical characteristics of the final product depend on the quality of the reagents and on the contaminants. Unlike cocaine HCl, methamphetamine HCl is volatile and can be smoked.[24] For cocaine to be smoked, it must be converted to pure cocaine alkaloid, commonly called crack (Table 1).

TABLE 1.—*Comparison of Methamphetamine and Cocaine*

Common Street Name	*Chemical Description*	*Characteristics*
Cocaine		
Coke, snow.....	D-Cocaine HCl and cutting impurities	Not volatile; administered through nasal or intravenous route
Crack, rock, free base.....	Pure alkaloid cocaine	Volatile; can be smoked
Methamphetamine		
Crank, speed....	D-, L-, or D/L-Methamphetamine HCl and impurities	Volatility dependent on impurities
Ice, crystal	D-Methamphetamine HCl (high purity, uncut)	Volatile; can be smoked

HCl = hydrochloride

The popularity of smoked methamphetamine is due to the immediate clinical effects of a euphoria resulting from the drug's rapid absorption from the lungs. Thus, the effect of intravenous use can be achieved without using needles. For several years, patients of one of us (B.H.) have described smoking methamphetamine-HCl powder or crystals by first placing the substance in a piece of metal foil molded into the shape of a bowl and then heating it over the flame of a cigarette lighter. The fumes then can be inhaled through a straw. Because of a more rapid and intense drug effect, these patients described a "high" distinct from that produced by snorting or ingesting methamphetamine. They also reported that smoking the drug produced a high lasting a shorter time than that experienced with other routes of ingestion. As would be expected when methamphetamine is smoked, the duration of action is similar to that produced with intravenous injection.

Clinical Pharmacology

Methamphetamine causes central nervous system (CNS) stimulation that may induce euphoria, increase alertness, intensify emotions, alter self-esteem, and allegedly increase sexuality.[9] At the cellular level, dopamine is displaced from specific nerve terminals, causing hyperstimulation of dopaminergic receptor neurons in the synaptic cleft.[25,26] These hyperstimulated neurons in turn stimulate various CNS pathways and the sympathetic nervous system. Direct peripheral and organ stimulation by methamphetamine may also occur. The half-life of amphetamines ranges from 10 to 30 hours, depending on urine pH.[27,28] Methamphetamine has greater CNS efficacy compared with D-amphetamine, presumably because of increased CNS penetration.[29]

The euphoric effects produced by methamphetamine, cocaine, and various designer amphetamines are similar and may be difficult to differentiate clinically. The findings from many studies in animals and humans support these observations. A distinguishing clinical feature is the longer half-life of methamphetamine, which may be as much as ten times longer than the half-life of cocaine.[16,30] Nevertheless, more recent studies in animals with D-amphetamine and cocaine suggest differences in underlying CNS mechanisms between the two types of stimulants.[31-33]

Because methamphetamine is purchased illicitly and may be mixed with both inert and other toxic substances, the clinical observation of toxic effects is more relevant than an estimate of ingested dose. In addition, tachyphylaxis occurs with methamphetamine use, and long-term users tolerate higher doses with fewer symptoms. Fatalities have been reported after ingestions as low as 1.5 mg per kg of methamphetamine,[34] whereas long-time abusers in whom tolerance to the drug develops may use as much as 5,000 to 15,000 mg per day.

Toxic Effects

In toxic doses, methamphetamine induces unpleasant CNS symptoms such as agitation, anxiety, hallucinations, delirium, and seizures; death can occur.[16,35-37] Cardiovascu-

lar symptoms such as chest pain, palpitations, or dyspnea can also develop. There is evidence that high doses of methamphetamine induce irreversible CNS-destructive changes.[38,39]

Methamphetamine can both induce an acute toxic psychosis in previously healthy persons and precipitate a psychotic episode in those with psychiatric illness.[40] Nearly all patients presenting to emergency departments with toxic effects require referral to a psychiatric center. In the past, psychiatric disorders were diagnosed before addiction in many amphetamine users. This has not been the case recently, however.[41] An acute and dramatic choreoathetoid disorder can also be triggered by amphetamines.[42] Hyperthermia may result from CNS-induced abnormalities, seizures, or muscular hyperactivity. Rhabdomyolysis may occur secondarily.[15]

Cardiovascular manifestations of amphetamine toxicity include hypertension, tachycardia, atrial and ventricular arrhythmias, and myocardial ischemia.[43,44] Chest pain has been reported in some persons but usually without electrocardiographic changes. The incidence of toxicity-induced cardiovascular symptoms is less than with cocaine.

Patients who are unconscious on arrival at an emergency department or who have been found unresponsive may have used methamphetamine. In some of these persons, lack of responsiveness may be due to the use of other drugs such as opiates. Other patients may be unresponsive because of intravenous methamphetamine use. Hypothesized reasons for this effect include seizure, hypotension, a reaction to a contaminant, or undescribed effects of intravenous amphetamine. Other disorders that have been described include cerebrovascular accident due to hemorrhage or vasospasm.[45,46]

Treatment

Despite methamphetamine's ability to induce significant CNS and cardiovascular stimulation, relatively few patients who present to emergency departments for acute intoxication require pharmacologic intervention.[7] In many emergency departments, patients are not treated for agitation unless they could harm themselves while jerking or tearing at their restraints. These hyperactive or agitated persons can be treated with haloperidol or diazepam, and all appear to respond well to treatment with either drug.

Central Nervous System Toxicity

Haloperidol and diazepam are well-established agents that antagonize CNS symptoms. Haloperidol, a dopamine-2 blocking agent, can specifically antagonize the central effects of methamphetamine. Studies in animals have shown the superiority of haloperidol to diazepam in protecting against death.[33] Multiple clinical reports attest to the efficacy of haloperidol.[7,14,15] In addition, on receiving intravenous haloperidol, patients who sustain the acute choreoathetoid syndrome may have symptoms quickly resolve. Haloperidol has an advantage over diazepam in that it can be given intravenously or intramuscularly. Recommended doses are 2.0 to 5.0 mg initially, with additional dosing titrated to clinical response.

Diazepam, a benzodiazepine that enhances γ-aminobutyric acid neurotransmission, affects methamphetamine intoxication through a nonspecific sedative action. Diazepam is highly effective in antagonizing the stimulant toxic effects of cocaine but not amphetamines in animals.[31,33] Despite this observation, diazepam is used successfully to control clinical symptoms.

Cardiovascular Effects

Many antihypertensive agents and β-blockers are effective in reversing methamphetamine-induced cardiovascular symptoms. For treating an amphetamine-induced hypertensive crisis, agents such as phentolamine or nitroprusside provide efficacy. Blood pressures may also respond indirectly to the sedating effects of haloperidol. Calcium channel blockers have been used successfully in some emergency departments.

Many cases of methamphetamine toxicity can be managed conservatively. The clinician should confirm suspected amphetamine use through a urine toxicologic analysis. Other conditions that may produce symptoms—such as infections, metabolic disorders, or use of other drugs—should be excluded. Patients should receive volume replacement as determined by hydration status. In past studies, as few as 10% of the patients presenting to emergency departments required admission, and those who were admitted to hospital were generally discharged within two days. In the past, vital signs were thought to be an indicator of the severity of intoxication, with a temperature above 40°C being a poor prognostic sign. In one series, however, there was no significant difference in vital signs between those admitted and those not admitted.

Summary

In conclusion, methamphetamine is a dangerous drug that matches or supersedes cocaine in inducing symptoms of euphoria. The volatility of methamphetamine appears similar to that of crack cocaine, and thus it can compete with cocaine for use by long-term or recreational users wanting a rapid high through inhalation. Unlike that of cocaine, the half-life of methamphetamine may produce exceptionally long-lasting toxic effects. Clinicians should consider the possibility of methamphetamine use or abuse in any patient presenting with psychosis, violence, seizures, or cardiovascular abnormalities.

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Counseling Patients Seropositive for Human Immunodeficiency Virus

An Approach for Medical Practice

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Persons at risk for infection with the human immunodeficiency virus are being encouraged to learn their serostatus. While such knowledge can help patients seek appropriate medical care, it can also be distressing. We describe an approach, based on crisis counseling, for physicians to use in working with patients infected with HIV. It can help physicians in assisting patients with emotional reactions to the diagnosis as well as in directing patients to manage practical issues of concern. Methods for discussing safer sex or injection practices are also presented.

(Coates TJ, Lo B: Counseling patients seropositive for human immunodeficiency virus—An approach for medical practice. West J Med 1990 Dec; 153:629-634)

Testing for antibodies to human immunodeficiency virus (HIV) infection benefits both persons at risk and society as a whole.[1-6] Persons who test positive can receive appropriate prophylaxis and treatment, such as zidovudine (AZT) and aerosol pentamidine.[7,8] Recent evidence that even asymptomatic seropositive persons will benefit from treatments will encourage more persons at risk to seek counseling and HIV testing.[9] Seropositive persons can also act to prevent the spread of infection to others.[4,6,7,10-12] But HIV testing may have devastating consequences, including stigmatization, discrimination, and the loss of jobs, insurance, medical benefits, and significant relationships.[13] In coping with their diagnosis, seropositive persons may suffer stress, anxiety, and depression, at least in the short term.[14-16]

In counseling seropositive persons, health care professionals must respond to patients' emotional reactions and help them cope with specific problems. Not all issues can be discussed at one visit. With a new seropositive patient, physicians in the first few visits can convey their willingness to provide ongoing care and to discuss emotions and feelings. Specific issues can be discussed in more detail at subsequent visits.

The Crisis Counseling Model

Patients and health care workers alike may feel overwhelmed and helpless after a positive HIV test result. Crisis counseling provides a model for health care workers to help seropositive patients deal with both emotional and practical problems. It asserts that it is important for patients to experience, express, and receive empathy for emotions and to make specific plans for coping. The counselor's goal is to allow emotions to be expressed (as long as they do not overwhelm the patient) and then to help the patient make specific plans. Many health care professionals think that they must "do something" for every problem brought to them by their patients. But patients may want only an opportunity to express their emotions to a safe and empathic listener. Furthermore, discussions of coping with specific problems are likely to be more fruitful after patients have had an opportunity to express their emotions and fears.

Emotional Reactions

With newly diagnosed seropositive patients, health care professionals need to be gentle and compassionate; allow patients to express their feelings, reactions, and concerns; and convey concern for the patients' emotional state. While no magic formula can change the prognosis or prevent the emotional distress, health care professionals can help patients cope with bad news. Nonjudgmental listening and making empathic statements such as *I can imagine that this feels overwhelming to you,* will help. Talking about reactions and fears can reassure patients that their reactions are a natural response to a life-threatening diagnosis. Many patients benefit from referral to a mental health counselor. Ongoing therapy can be provided if it is indicated; otherwise, the mental health professional can be contacted later as needed.

Uncertainty and Anxiety

Although many people get tested to resolve uncertainty about whether they are infected, a positive test result creates additional uncertainty. Whereas persons infected with HIV will probably die prematurely,[7] a positive test result does not predict when complications or clinical acquired immunodeficiency syndrome (AIDS) will develop. This uncertainty should be acknowledged: *Most people who test positive are upset because they don't know what will happen to them.*

Patients may ask how long they will be well, how long they will live, or what will happen next. They may ask questions having two different levels. On one level, they may request medical information. If so, physicians should attempt to provide it or refer them to community resources. Distress is alleviated if patients are well informed about their disease and the latest therapeutic developments.[17] On another level, questions may reflect underlying emotions. Patients may be asking, "Will I be okay? Who will take care

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Preparation of this work was supported in part by National Institute of Mental Health (NIMH)/National Institute on Drug Abuse AIDS Center grant No. MH42459, NIMH grant No. MH39553, and the Robert Wood Johnson Foundation.

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
HIV = human immunodeficiency virus
IV = intravenous

of me if I get sick? Will I be dependent on others?" While health care professionals cannot give a definite prognosis, they can listen to patients' concerns and react supportively. They can also reassure their patients that they will be there and provide the best care possible.

Common symptoms of anxiety include sleeplessness, fatigue, lethargy, loss of libido, difficulty with memory and concentration, hyperactivity, irritability, tremors, rapid heart rate, sweating, shortness of breath, nausea, diarrhea, and pain.[18] These nonspecific symptoms, of course, can also be caused by the HIV infection. Asymptomatic patients who experience these reactions immediately after diagnosis should be encouraged to express their underlying emotions. An empathic response from the physician can reassure patients that they have been heard and that their reactions are normal. In severe cases, a short-term course of antianxiety medications might be appropriate. Patients who do not experience these reactions may be warned that they commonly occur.

Anger

Patients may be angry at getting a fatal illness, frustrated over the lack of treatments, and upset over discrimination. Allowing them to express their anger may be helpful. Health care workers may only be able to assure patients that they are doing the best they can, but such reassurance may be helpful and healing. Health care professionals may also feel frustrated over their inability to cure the disease or over a limited access to drugs. It may be helpful for patients to hear such feelings.

Betrayal

Seropositive persons may feel betrayed and violated if they were infected by a partner whom they did not suspect of being infected. They may feel ambivalent about discussing the infection with suspected partners. Perhaps later joint sessions might be scheduled with the suspected partner to discuss the positive result and its implications for their relationship. It is also important to consider the possibility that exposure did not occur through that particular partner but rather through another means.

Patients may feel angry at persons (or a class of persons) who may have infected them. After listening to these emotions, physicians should explore whether violence is being considered. If a patient has specific plans for violence and has the means to carry them out, the physician may need to warn specific persons threatened and evaluate the patient for involuntary admission to hospital.

Denial

Some people cope with positive HIV test results by denying that they are positive. The physician may need to challenge the denial if it leads the patient to self-harm or to expose others to the virus. A challenge can begin gently: *I wish that you were not infected.* Misconceptions should be corrected. *It's a shame that antibodies to HIV don't prevent infection, the way antibodies protect against other diseases.* In some cases, repeating the test may help the patient accept the result. In this way, confrontation can be escalated until the patient is ready to accept the significance of the positive test result.

TABLE 1.—*Symptoms of Major Depression*

Poor or increased appetite
Insomnia or hypersomnia
Psychomotor retardation or agitation
Loss of interest or pleasure in activities or loss of libido
Fatigue
Feelings of worthlessness, self-reproach, or guilt
Decreased concentration
Recurrent thoughts of death or suicide

Fear

Simple, straightforward questions can elicit fears: *What are your major fears about HIV infection?* or *When you think of HIV infection or AIDS, what scares you the most?* Seropositive persons may fear some specific issues, such as a loss of relationships, problems with employment or insurance, or a loss of confidentiality. Alternatively, they may fear declining health, distress to friends and relatives, a prolonged, painful death, or uncertainty about the afterlife. Their distress is likely to increase as more of their friends struggle with and die of AIDS.[19,20] Health care professionals should acknowledge that these fears are legitimate. Referral to mental health resources may be needed if the patients' responses are extreme or if adequate care cannot be given by primary care givers. Concrete planning will also help patients to cope.

Regret

Patients may have feelings of regret or guilt for past behavior. It is important for physicians to emphasize that AIDS is not a punishment for homosexuality, intravenous drug use, sexual behavior, or any other action.

Depression

Major depression is more common in HIV-infected persons than in the general population.[20] Physicians must assess the severity and duration of depression.[18] In major depression, at least four of the symptoms presented in Table 1 are present nearly every day for at least two weeks. If major depression is present, treatment with antidepressant therapy or psychotherapy[21] may be indicated. Psychiatric consultation may help minimize drug side effects likely to be exacerbated in HIV disease.

Persons with AIDS are at increased risk for suicide.[15,16,22,23] If a patient is severely depressed or expresses thoughts of death, the physician needs to conduct a complete suicide evaluation, asking about suicidal ideas, specific plans, the ability to carry out the plans, and intentions to carry them out. Direct and simple questions are best, such as, *Do you find yourself thinking about dying or death? Can you tell me what you have been thinking? Do you think about taking your own life? How would you do it?* If the patient has ideation, plans, ability, and intentions, the physician should consider whether referral to a mental health professional or recommendation for voluntary or involuntary hospital admission is indicated.

Some patients consider suicide not because of depression but as a realistic alternative to intolerable terminal illness. Some patients may feel that life has lost its meaning. The strategy of "pacing and leading" is helpful. The physician can ask the patient to define more precisely when life would become intolerable. Then the physician can watch for these signs, question the patient further at this time, and ask if the limits can be defined still further. These discussions often lead the patient to shift the question from

when life becomes intolerable to what gives life meaning in the face of terminal illness. Some terminally ill patients may make a "rational" decision to commit suicide despite such discussions. Physicians need to anticipate their own responses: What will they do when asked to write a prescription for a lethal dose of medications? Will they resuscitate the patient after an overdose? The ethics of assisted rational suicide are controversial. While abetting suicide is illegal in most states, it may not be immoral for physicians to assist a patient in rational suicide.[24]

Delayed Reactions

The full effects of the test results may not be felt until a person has had time to reflect. Health care professionals should inquire about feelings at each visit. They can encourage patients to talk about their reactions, schedule additional visits as needed, and inform patients of resource agencies in the community.

Unexpected Positive Results

A positive HIV test result may be unexpected. A person may not have engaged in high-risk behavior for a considerable time. Some patients may not even know that they had had exposure to HIV, as through blood transfusions. The resulting reactions may be more extreme than in persons who expected positive results. Persons who acquired HIV by transfusions might feel stigmatized by a disease that they share with intravenous drug users, homosexual men, or members of an ethnic minority group.

Negative Test Results

Whereas negative results may bring relief, they do not necessarily end a patient's anxieties. Because HIV antibodies may not be detected early in HIV infection, seronegative persons with recent high-risk behaviors should be retested in six months. In addition, some persistently seronegative high-risk persons have been found to be infected.[25,26] Seronegative persons might also experience "survivor guilt": the feeling (similar to that experienced by survivors of the Holocaust) that they do not deserve to be spared. The anxiety experienced by seronegative patients needs acknowledgment, as does their need for continued follow-up care. Physicians should emphasize the importance of avoiding high-risk behaviors.

Reactions by Health Care Professionals

It is important for health care professionals to be aware of their own personal responses to specific types of patients and behaviors. Negative reactions towards patient behaviors are not restricted to HIV disease. Diseases such as coronary artery disease and cancer have strong behavioral risk factors, such as smoking or diet. It may be helpful for care givers to discuss with colleagues specific types of patients or interactions with those patients. Empathy for patients and a willingness to care for them does not require or imply an approval of everything about them. Health care professionals should react to patients' current suffering, not to their previous behaviors. Most important, personal feelings about patients should not impede providing high-quality care.

Specific Plans for Coping

After patients have had an opportunity to express their emotional reactions, health care professionals can help them make specific plans for coping. Making specific plans can give patients a sense of control over their illness. Care givers should be familiar with community agencies providing support services for HIV-infected persons and make referrals as needed.

Relationships and Social Support

Seropositive persons may fear social ostracism, a loss of intimate relationships, and difficulty in forming new relationships. They may fear that partners will get angry or reject them if they disclose their diagnosis. But partners should have a choice about having sexual relations with someone who is seropositive; relationships and intimacy must be built on trust. Persons who are seropositive should notify their sexual and needle-sharing partners about their diagnosis, just as they would want others to notify them. In research studies, most have said that they would notify partners if they were found to be seropositive.[27]

The physician can question patients directly about fears of partner reactions: *What do you fear most about telling others about your HIV infection?* From there, it is possible to deal with more specific plans. *Let's think of some specific words you can use to tell your partner about this. How will you start the conversation?* Other issues can be anticipated: *What if [he, she] reacts with alarm, or anger, or crying? What will you say?* Such planning and role playing can help the patient carry out a difficult task.

Some patients may fear that notifying a partner will destroy a long-term relationship. The physician can ask, *Won't your partner find out eventually, especially if you get sick?* The physician can also help the patient appreciate that the relationship will probably suffer more if the partner is not told immediately. *How do you think [he, she] would feel if [he, she] found out later that you hadn't told [him, her] right away?*

Some patients believe they do not need to tell the partner that they are seropositive,[27] provided they take steps to protect the partner. For instance, some couples are already using condoms. Unless partners know about the positive test result, they cannot make informed decisions about sexual practices, the relationship, or HIV testing. While condoms provide substantial protection, they can be defective or used incorrectly.[28,29]

Physicians should try to persuade seropositive patients to notify partners or to allow others to do so. If a patient refuses, the physician faces an ethical dilemma about whether to override the confidentiality of medical information to protect an identified third party from serious harm.[30] When partners have no reason to suspect that they are at risk for HIV, the arguments for notifying are particularly strong.[31] Several states, including New York and California, now permit (but do not require) physicians to notify sexual and needle-sharing partners of seropositive persons when the index case does not agree to do so. Alternatively, the physician can ask public health officials to notify contacts. Physicians who plan to notify partners should warn patients of this intention so that patients can notify partners personally if they prefer. The identity of the patient should not be disclosed to the partner. Public health officials who carry out partner notification for other sexually transmitted diseases do not disclose the identity of the index case,[32] merely saying that *Someone who loves you wants you to know that you are or have been exposed to HIV infection.*

The decision about whom else to tell is up to the affected person. It depends on the strength of relationships, the expected reactions from others, and the purpose in telling them. It is probably best to begin with one or two close friends or relatives, assess their reactions, and then gradu-

ally tell others from whom the patient might want help or support.

Advice for Safer Sex

Seropositive patients need explicit and specific advice about the sexual transmission of HIV. Essential advice for "safer sex" is presented in Table 2. The term "safer sex" is ambiguous[33]; health care professionals should distinguish between behaviors that eliminate the risk of HIV transmission and those that merely reduce it. Explicit instructions about condom use (Table 3) are necessary because they frequently are used incorrectly.[34] Care givers should use language patients can understand, such as "rubbers" or "sheaths" for condoms. The worker might elicit patients' preferred terms and use them. Advice works better when it is concrete, tailored to the individual, and reinforced at subsequent visits. To achieve this, health care professionals need to understand patients' sexual habits. They should ask about:

- The patient's sexual preferences. *Do you have sex with women, men, or both?* It is not possible to take proper care of a seropositive patient without knowing this information. Patients are likely to be more honest about their preferences if they feel they can trust their physician and if they feel that their activities are viewed as common. *Many of my patients have sex with men, women, or both.*
- The patient's specific sexual practices. *To take care of you well, I need to know what kinds of sexual activities you prefer and engage in.* Care givers should ask patients about specific high-risk practices: *Do you practice anal sex? Oral sex? In anal and oral sex, are you insertive, receptive, or both?* It is important to keep in mind that many heterosexuals practice anal intercourse[35] and that men who have sex with men engage in both insertive and receptive practices.

Information expressed by a physician may not be heard by a patient. The only way to determine what has been retained is to ask the patient to repeat it: *Sometimes I'm not very clear explaining things. To check whether I covered everything, could you repeat back what I just said?*

The health care worker should also discuss whether the patient feels that recommendations for safer sex are practical. If not, the issues need to be discussed further: *Some people don't think that condoms will work for them. Do you feel this way?* More specific concerns can then be addressed, such as fears that condoms will reduce pleasure or spontaneity: *Many of my patients have found that they can have fun and be fully satisfied with condoms. You should try them.* Women may have particular difficulties bringing up the issue of condoms with partners: *Some women find it difficult to raise the issue of condoms. Is it difficult for you?* Others may not feel comfortable purchasing condoms, carrying them, or keeping them at home.

Many health care professionals may feel uncomfortable about discussing sexual matters explicitly. While the US Surgeon General, Koop wrote,

> My moral and religious background has made it difficult for me, as it may be for you, to discuss sexual issues in public. The frankness of my report on AIDS in October 1986 shocked many. I had no choice as a health officer when the alternative is almost-certain death.[34]

A national survey revealed that only 15.4% of respondents had discussed AIDS with their physicians, and only 22% had discussed their sexual behavior with their physicians.[36] Most (90%) said that they would feel comfortable discussing AIDS, and 84% said that they would feel comfortable discussing sexual activity. On a more practical level, health care professionals may want to practice asking such questions with colleagues so that they seem routine. Similarly, care givers might consider whether their own values regarding sexuality are making them less effective as health care professionals. Regardless of personal values and beliefs, a judgmental attitude is likely to be counterproductive, making it less likely that patients will heed the advice to reduce their high-risk behaviors that transmit HIV infection to others.

Some persons need to be reassured that intimate relationships are still possible. In some cases, it might be helpful to put a patient's situation into a larger context: *Because you are antibody-positive, you might feel isolated. But you are not alone. There are many people in your situation. If you are interested in finding a partner, that should still be possible.*

Intravenous Drug Users

Many health care workers are pessimistic about treating intravenous (IV) drug users. Problems associated with IV drug use, such as poverty, crime, prostitution, or homelessness, may seem overwhelming. The use of cocaine, which is associated with HIV infection and with the heterosexual transmission of HIV, is particularly refractory to treatment.[37,38] Furthermore, drug treatment slots are limited, and waiting lists may be long. Intravenous drug users have responded to some kinds of drug treatment and AIDS-prevention programs, however.[39] High-dose methadone programs have been reported to have more success than drug-free treatment programs.[40,41] A case-management approach may offer assistance with bureaucratic, financial, and housing problems, coordinate medical care with drug treatment, and provide counseling about preventing relapse.[42]

Table 4 presents key advice to intravenous drug users. While the ultimate goal is to rehabilitate IV drug users, it is essential (and realistic) to recognize that many of them will continue to inject drugs and to provide counseling for them. In San Francisco, more than half of IV drug users report that

TABLE 2.—*Advice for Safer Sex*

Seropositive persons should inform their partner they are seropositive
Celibacy, mutual masturbation, and other nonpenetrative sexual activities carry no risk of transmitting HIV
While condoms reduce HIV transmission, they are not foolproof
HIV can be transmitted to the insertive as well as receptive partner
The risk of transmission during oral sex is not known, but is slight

HIV = human immunodeficiency virus

TABLE 3.—*Instructions for Condom Use*

Roll the condom onto the penis after it becomes erect but before it comes into contact with the partner
Leave a small air space at the tip
Use the condom throughout the sex act
Withdraw the penis before the erection is lost
Use a new condom with each sexual act
Use latex condoms
Use water-based lubricants, not oil-based ones
Do not store condoms near extreme heat or cold

TABLE 4.—*Advice for Intravenous Drug Users*

Drug treatment programs work; get into one
Do not "shoot" drugs
If you do shoot, do not share the "works"
If you do share the works, clean the works with bleach before you use it

they are cleaning needles and syringes with free bleach distributed through a citywide program.[43] In addition, because IV drug use is associated with heterosexual and perinatal HIV infection, counseling about safer sexual practices is crucial.

HIV Infection in Women

Women are at risk for HIV infection through intravenous drug use and sexual contact with infected men, most of whom are IV drug users. Infection with HIV in women is particularly tragic because about 30% of infants born to seropositive women will be infected with the virus.[40]

Seropositive women have special needs.[44] They may need child care and support groups. They also need gynecologic and obstetric care, both for other sexually transmitted diseases and for reproductive health care. Counseling and education are essential for seropositive women to make informed choices about childbearing. Knowledge of HIV seropositivity per se, however, has little influence on decisions about childbearing among inner-city female IV drug users.[45] Many such seropositive women continue pregnancies or have subsequent pregnancies. Close medical follow-up during pregnancy is needed because HIV infection may progress during this time.[45] Furthermore, drug treatment and counseling during pregnancy are vital because maternal IV drug use causes additional risk to infants. In addition, plans should be made in case symptoms of HIV disease develop in the mother or child.

Medical Care

Seropositive persons should be urged to seek regular medical care. They should have prognostic markers measured, such as CD4 counts (and p24 antigen and β_2-microglobulin, if available).[9] In some situations, the use of aerosol pentamidine or zidovudine is effective in preventing opportunistic infections or prolonging survival. In addition, the timely diagnosis and treatment of opportunistic infections require good primary care. As other drugs are found to be effective, the importance of regular medical care will be even greater. Even among intravenous drug users, compliance with medical follow-up and treatment may be acceptable.[46,47] Providing patients an active role in treatment decisions may engender a sense of hope and control.

Confidentiality

Physicians, nurses, and dentists should know about a patient's HIV diagnosis so they can provide sound advice, timely diagnosis, and effective treatment. Generally a patient will receive better care when HIV infection is documented in the medical record because optimal care requires interdisciplinary cooperation. Strict care must be taken to prevent an inappropriate disclosure of information contained in medical records, which may result in discrimination and loss of employment or insurance.[1]

What If the Disease Progresses?

The percentage of seropositive persons who progress to AIDS has been found to increase with longer follow-up of cohorts.[7,48,49] After the initial reaction to a positive HIV test result, physicians should encourage patients to develop strategies for dealing with disease progression. Issues to consider include the following:

- How will I cope with disability? Where will I live? What financial resources will be available? Will I have adequate insurance?
- Who can I rely on if I get sick? Who will take care of my responsibilities—such as child care—if I become sick?
- Who will make decisions about my health care if I become incompetent?
- What life-sustaining treatment will I want or not want if illness progresses?

Although physicians cannot be experts on all these issues, they can encourage seropositive patients to make plans and refer them to appropriate community resources.

Conclusion

While caring for persons infected with HIV may be difficult and stressful, it can also be stimulating and rewarding.[50] The counseling strategies recommended here may help to enhance patients' quality of life while making the medical management of the patient more effective.

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Special Editors

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This article is one of a series on topics in primary care in which common diagnostic or therapeutic problems encountered in primary care practice are presented. Physicians interested in contributing to the series are encouraged to contact the Special Editors.

Conferences and Reviews

Hypercalcemia in Malignancy

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The pathogenesis of hypercalcemia in malignancy has been enigmatic until recent years. Since the realization in 1980 that bioassays for parathyroid hormone detected a cross-reacting substance in malignancy, progress has been remarkably rapid. A parathyroid hormone-related protein was purified and identified by molecular cloning as a 141-amino acid peptide with limited homology to parathyroid hormone itself. Nonetheless, both peptides activate the parathyroid hormone receptor to produce hypercalcemia. It is now clear that the parathyroid hormone-related protein is the cause of hypercalcemia in most solid tumors, particularly squamous and renal carcinomas. New assays for the hormone as well as the related peptide have greatly simplified the differential diagnosis of hypercalcemia. At the same time, new agents for the treatment of hypercalcemia are becoming available, most notably the bisphosphonate drugs.

(Strewler GJ, Nissenson RA: Hypercalcemia in malignancy. West J Med 1990 Dec; 153:635-640)

Hypercalcemia is among the commonest and most serious complications of malignancy. It occurs in 5% to 10% of all patients with cancer, threatening their independence and their survival. Yet the fascination of malignancy-associated hypercalcemia for endocrinologists has been even stronger than these demographics can easily explain. A half century of study has been rewarded in the past decade by some understanding of the chemistry and biology of hypercalcemia, and the intuition that hypercalcemia is an endocrine disorder has proved correct. In this review we will focus on developments since 1980 in the pathophysiology, diagnosis, and treatment of hypercalcemia.

Clinical Features

Hypercalcemia typically appears late in the course of malignancy. It presents with anorexia, nausea, polyuria, confusion, or coma. Evidence of malignancy is seldom subtle when hypercalcemia occurs: the tumor is already known or readily evident in at least 98% of patients.[1] Often hypercalcemia ushers in a final phase of the disease. The median survival of hypercalcemic patients is only 30 to 90 days.[1,2]

Solid Tumors and the Parathyroid Hormone-Related Protein

The solid tumors most often associated with hypercalcemia are lung carcinoma (25% of all cases); breast carcinoma (20%); squamous carcinomas of the head, neck, esophagus, or female genital tract (19%); and renal carcinoma (8%).[1] Of lung carcinomas, 23% of epidermoid (squamous) carcinomas and smaller fractions of large-cell carcinomas or adenocarcinomas will produce hypercalcemia, but hypercalcemia is rare in small-cell lung carcinoma.[3] Overall, about a third of tumors complicated by malignancy-associated hypercalcemia have a squamous histology.

Because malignancy-associated hypercalcemia has some features of primary hyperparathyroidism, such as hypophosphatemia, the possibility that a parathyroid hormone (PTH)-like substance was involved had long been considered. Yet patients with malignancy and hypercalcemia generally have normal PTH levels.[4,5] The key step in the understanding of hypercalcemia in solid malignant tumors was the development of bioassays for parathyroid hormone. About 80% of patients with malignancy-associated hypercalcemia (including nearly all the patients with squamous or renal carcinomas) have increased urinary levels of cyclic adenosine monophosphate (AMP).[4,5] Increases in urinary cyclic-AMP levels were hitherto considered highly specific for hyperparathyroidism, reflecting the activation by PTH of adenylyl cyclase in the renal tubule, resulting in increased extrusion of cyclic AMP into the urine in hyperparathyroidism. The data thus suggested that a humoral, nonparathyroid substance was activating renal PTH receptors coupled to the synthesis of cyclic AMP. It was clear that assays to detect PTH-like bioactivity in vitro could be used to identify and purify the putative PTH-like substance.

The data on urinary cyclic AMP could be correlated with other features, neatly dividing hypercalcemic patients by the histologic features of their tumor. Patients having any of the solid tumors (other than breast carcinoma) fell into the group with high levels of urinary cyclic AMP. Multiple myeloma, lymphoma, and most cases of breast carcinoma were associated with a reduction in urinary cyclic-AMP levels, consistent with the suppression of PTH by nonparathyroid hypercalcemia.

Using assays of adenylyl cyclase activation in bone or kidney cells for their detection, PTH-like peptides were subsequently purified from squamous lung, breast, and renal carcinomas,[6-9] and molecular cloning proved that the peptides produced by these different tumors were identical.[10-12] The tumor-derived protein has predicted isoforms of 139, 141, and 173 amino acids, compared with 84 amino acids in PTH. (The isoforms, which arise from alternative RNA splicing at the carboxyl terminus of the peptide,[12,13] have a common sequence through amino acid 139.) The tumor peptide strongly resembles PTH only at its amino terminus (Figure 1), with 8 amino acid identities among the first 13

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This work was supported in part by the Medical Research Service of the US Department of Veterans Affairs and by National Institutes of Health grants CA34738 and AM35323.

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ABBREVIATIONS USED IN TEXT

AMP = adenosine monophosphate
IL-1 = interleukin 1
PTH = parathyroid hormone
PTHrP = parathyroid hormone-related protein

residues of the mature peptides. Thereafter, the two peptide sequences have little in common. The amino-terminal identities, however, together with similarities of gene structure,[14-16] indicate that PTH and the tumor-derived peptide are the products of a common ancestral gene. Hence, the tumor-derived substance has provisionally been named the PTH-related peptide (PTHrP); it is also called PTH-like peptide and humoral hypercalcemic factor.

As with PTH, amino-terminal peptides composing the 1 to 34 sequence of PTHrP are fully active at the PTH receptor.[17-21] What is surprising is that PTH and PTHrP are equipotent for receptor binding and for most of their acute effects, despite the divergence of their primary sequences in the 14 to 34 domain that is required for binding. In fact, PTH 14 to 34 and PTHrP 14 to 38, fragments with entirely divergent sequences, both compete for PTH-receptor binding, albeit weakly.[22] This is an unusual and important example of shared function, and presumably shared secondary and tertiary structure, in the setting of a remote relationship of primary amino acid sequence. As a first step toward understanding the tertiary structural features of these peptides, the structure of PTHrP 1 to 34 has recently been determined using two-dimensional nuclear magnetic resonance.[23]

It may be surmised from its binding to the PTH receptor that PTHrP would mimic all the classic acute effects of PTH. In the kidney, PTHrP or amino-terminal peptides of PTHrP indeed produce phosphaturia,[17,24-26] hypocalciuria,[24,27,28] and activation of 25-hydroxyvitamin D-1α-hydroxylase, stimulating the synthesis of 1,25-dihydroxyvitamin D.[17,29] Moreover, PTHrP is approximately equipotent with PTH in producing bone resorption and hypercalcemia.[17,27,30,31]

As a potent hypercalcemic and phosphaturic substance, PTHrP fulfills a major criterion to be satisfied by a mediator of hypercalcemia. Two subsequent findings strongly support the conclusion that PTHrP is the primary humoral mediator of hypercalcemia in solid tumors. First, serum levels of PTHrP by radioimmunoassay are increased in most hypercalcemic patients, including 71% of all patients with solid tumors and 85% of patients in whom hypercalcemia develops in the absence of bone metastases, but levels of PTHrP are normal in most normocalcemic cancer patients and in hyperparathyroidism (Figure 2).[32-34] The expression of PTH-like bioactivity,[35] PTHrP messenger RNA,[36,37] or immunoreactive PTHrP[38] in tumors is also correlated with the presence of hypercalcemia, although in one report immunoreactive PTHrP was detectable immunohistochemically in all squamous tumors studied.[39] Second, hypercalcemia is blocked by affinity-purified neutralizing antibodies to PTHrP in an animal model in which hypercalcemia is induced by the growth of human squamous tumors in nude mice.[40] Thus, PTHrP appears to be both necessary and sufficient to produce humoral hypercalcemia. This argues against the view that a concomitant secretion of other cytokines is required for tumors to produce hypercalcemia.

Even in patients with solid tumors metastatic to bone, it is probable that hypercalcemia often has a humoral basis. This conclusion flies in the face of conventional thinking that the osteolysis observed on x-ray films is the direct cause of hypercalcemia. The extent of bone metastases correlates poorly with hypercalcemia, however.[41] For example, among bronchogenic carcinomas, osseous involvement most frequently occurs in small-cell carcinoma (66%), but these patients rarely have hypercalcemia.[3] Moreover, of patients with clear evidence of humoral hypercalcemia—increased serum levels of PTHrP or increased urinary levels of cyclic AMP—bone metastases are also present in a third to a half.[4,32,33]

Nearly all patients respond to potent inhibitors of bone resorption—such as bisphosphonates (to be discussed later)—indicating that increased bone resorption is the primary pathogenetic mechanism of hypercalcemia produced by PTHrP. The effect of PTHrP to decrease renal calcium excretion is probably also important,[42-45] although it has been difficult to devise conditions to quantitate the relative contributions of bone resorption and hypocalciuria to the pathogenesis of hypercalcemia in humans. Part of the response to saline diuresis in cancer patients probably reflects a reversal of the hypocalciuric state induced by PTHrP. Also, the responsiveness to bisphosphonate therapy appears to be a function of tumor type and calcium excretion; it may be that patients in whom the secretion of PTHrP produces hypocalciuria are relatively (though not absolutely) resistant to bisphosphonates.[46,47]

Although a strong case can be made that PTHrP is the humoral mediator of hypercalcemia in solid tumors, some aspects of the syndrome of hypercalcemia remain to be explained. Plasma levels of 1,25-dihydroxyvitamin D tend to be low in patients with malignancy,[4,48,49] despite the initial effect of PTHrP to stimulate the synthesis of 1,25-dihydroxyvitamin D[17,18] and contrasting with the normal to high levels of 1,25-dihydroxyvitamin D occurring in pri-

	1				5					10					15			
PTHrP	Ala	Val	Ser	Glu	His	Gln	Leu	Leu	His	Asp	Lys	Gly	Lys	Ser	Ile	Gln	Asp
PTH	Ser	Val	Ser	Glu	Ile	Gln	Leu	Met	His	Asn	Leu	Gly	Lys	His	Leu	Asn	Ser

					30					25					20		Leu
PTHrP	Ala	Thr	His	Ile	Glu	Ala	Ile	Leu	His	His	Leu	Phe	Phe	Arg	Arg	Arg	Met
PTH	Phe	Asn	His	Val	Asp	Gln	Leu	Lys	Lys	Arg	Leu	Trp	Glu	Val	Arg	Glu	

Figure 1.—The amino-terminal amino acid sequence of the parathyroid hormone-related peptide (PTHrP) is compared with that of the parathyroid hormone (PTH).

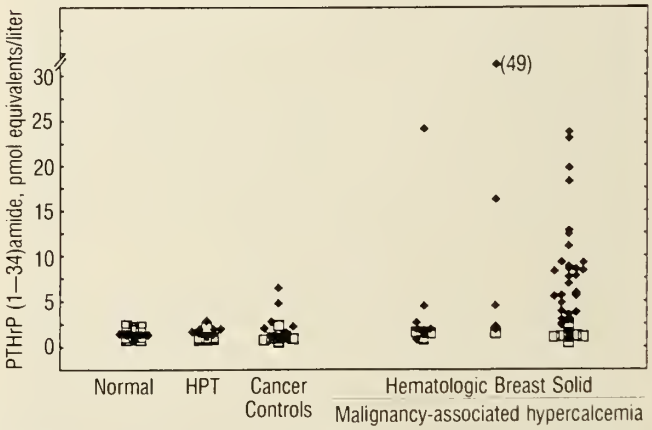

Figure 2.—Serum levels of parathyroid hormone-related peptide (PTHrP) are shown in normal subjects and in patients with hyperparathyroidism (HPT) or malignancy (reprinted with permission from Budayr et al[32]). Samples of undetectable levels are indicated by open squares and detectable levels by closed diamonds.

mary hyperparathyroidism.[4] Part of the explanation for this difference may come from the effect of hypercalcemia itself to suppress the production of 1,25-dihydroxyvitamin D, tending to counteract the initial stimulatory effect of PTH and PTHrP. By this mechanism a continuous infusion of PTH, in contrast to the effects of hyperparathyroidism, suppresses rather than stimulates 1,25-dihydroxyvitamin D levels.[50] It seems likely that either the pattern of secretion of PTHrP (continuous?) or associated ancillary factors[51] cause a greater suppressive effect of hypercalcemia on 1,25-dihydroxyvitamin D levels in malignancy than in primary hyperparathyroidism. Evidence has been reported for a tumor-derived suppressor of renal 1α-hydroxylase that is distinct from PTHrP.[51]

Increased bone resorption in malignancy-associated hypercalcemia is accompanied by a decrease in bone formation.[52,53] This uncoupling of bone resorption and bone formation contrasts with primary hyperparathyroidism. In hyperparathyroidism and most other resorptive states, bone formation is also increased, bone remodeling remaining coupled. Infusing PTHrP is variously reported to increase[54] or decrease bone formation.[55] Under conditions where PTH is anabolic for bone, PTHrP may be less so.[56,57] Yet the in vitro effects of PTHrP on the bone-forming cell, the osteoblast, are similar to those of PTH.[58] It remains to be determined whether the depression of bone formation in malignancy results from an intrinsic difference between PTH and PTHrP; from differences in the secretion of PTH and PTHrP (for instance, intermittent versus continuous); or from ancillary factors in malignancy such as illness, inanition, the decreased level of 1,25-dihydroxyvitamin D, or a concomitant secretion of other cytokines. Interleukin 1 is sometimes secreted with PTHrP[59,60] and can diminish bone formation.[61]

Physiologic Role of Parathyroid Hormone-Related Protein

The parathyroid hormone-related peptide is more than a henchman of the cancer cell; it is a new hormone. Owing to the route of its discovery, PTHrP is currently a hormone without a function, but it is likely that its physiologic role(s) is important. The PTHrP sequence has been deduced from cloning rat and chicken,[62-65] as well as human, genes and proves to be highly conserved—better conserved than that of PTH. The peptide is expressed in several normal tissues, including the epidermis,[39,62,66,67] pancreatic islets,[68] stomach,[67] adrenal glands,[67] and the brain.[69] The major role of PTHrP may be local rather than systemic. Its circulating level is considerably less than that of PTH,[32,33] suggesting that PTHrP may not participate in systemic calcium homeostasis under normal conditions. It may have a systemic role in certain physiologic circumstances, however.

The highest expression of PTHrP is in lactating mammary tissue, where it is under the control of prolactin.[62,70] Mammalian milk is the richest known source of PTHrP, containing 50 to 100 ng per ml, about 10,000-fold higher than the serum level.[71,72] It is thus possible that PTHrP has a local or systemic role in the regulation of neonates. There is also evidence to suggest that PTHrP is a regulator of placental calcium transport.[73,74] In addition, PTHrP is expressed in a variety of fetal tissues and can act as a differentiation factor in at least one model system, the F9 mouse embryonal carcinoma cell.[75]

The normal role of PTHrP is presumably different from that of PTH. The effect of PTHrP on placental calcium transport is reportedly not mimicked by PTH.[73,74] Synthetic PTHrP (1-36)amide, but not PTH, has transforming growth factor-like activity.[76] As the normal roles of PTH and PTHrP are apparently different, it might be surmised that a unique PTHrP receptor would have evolved. It is conceivable that the putative PTHrP receptor would recognize determinants in the 14 to 112 region, whose sequence is highly conserved but has no significant homology to PTH.[62-65] All the PTHrP receptors identified to date recognize PTH as well, however.

Hematologic Neoplasms

Hypercalcemia occurs in a third of patients with multiple myeloma and in 1% to 2% of patients with lymphoma and leukemia. These hypercalcemic patients almost always have bone involvement, in contrast to patients with solid tumors. It is postulated that the local release of cytokines with bone-resorbing activity is the commonest cause of lytic bone lesions and hypercalcemia in multiple myeloma and lymphoma, but this is not proved. The term "osteoclast-activating factor" was formerly used to identify the bone-resorbing activity in supernatants of normal or malignant leukocytes. This term is no longer appropriate, now that individual cytokines can be identified. Cytokines with bone-resorbing activity include interleukin 1α (IL-1α), interleukin 1β (IL-1β), tumor necrosis factor-α, tumor necrosis factor-β (also called lymphotoxin), and transforming growth factor-α.[77] Given parenterally in rodents, these are weak hypercalcemic agents, consistent with a predominantly local role in lymphoma and myeloma.[78-81] It is unclear which of them may be involved in local hypercalcemia. The bone-resorbing substance in normal monocyte supernatants is IL-1β.[82] Myeloma cell supernatants reportedly induce bone resorption in vitro by secreting large amounts of IL-1β.[83,84] Other workers, however, have reported that the bone-resorbing factor of myeloma cells is lymphotoxin (tumor necrosis factor-β).[85] Determining which factors actually produce local osteolytic hypercalcemia (as opposed to bone resorption in vitro) will require the use of neutralizing reagents for individual cytokines in a suitable animal model or in patients. Unfortunately, no animal model of hypercalcemia induced by local osteolysis is currently available.

Other mediators are also associated with hypercalcemia in malignant hematologic disorders. Some lymphomas apparently produce 1,25-dihydroxyvitamin D as a mediator of hypercalcemia.[86,87] Although the original studies suggested this was an uncommon occurrence, in a recent series high levels of 1,25-dihydroxyvitamin D were found in 47% of patients with lymphomas.[88] Some cases of multiple myeloma are characterized by increased serum levels of PTHrP[32] or increased urinary cyclic AMP.[89] Hypercalcemia occurs in two thirds of cases of the adult T-cell leukemia syndrome, which is caused by the retrovirus human T-cell lymphotropic virus type 1. Patients with hypercalcemia have increased urinary levels of cyclic AMP,[90] and the tumor cells have been shown to produce a PTH-like substance in vitro.[91,92] Although adult T-cell leukemia cells also produce IL-1[93] and rarely 1,25-dihydroxyvitamin D,[86,94] the probable cause of hypercalcemia in this syndrome is PTHrP.

Differential Diagnosis

Even in a patient with a known malignant tumor, the differential diagnosis of hypercalcemia must be considered. Primary hyperparathyroidism is prevalent enough (about 3 cases per 1,000 in women older than 40) to occur in patients who also carry the diagnosis of cancer. In the past, making the distinction between hyperparathyroidism and malignancy has often been a challenging subject for clinicopatho-

logic conferences. One reason for the difficulty was that most sensitive PTH assays (directed towards midregion or amino-terminal determinants) detected a cross-reacting substance in malignancy.[95] This finding was reasonably taken as evidence that the PTH-like factor in malignancy was immunologically similar to PTH itself. But PTHrP has no sequence homology to the midregion of PTH, and purified PTHrP does not cross-react in midregion assays for PTH. Thus, the explanation for this highly reproducible result is uncertain.

The challenge of detecting hyperparathyroidism in the presence of malignancy has been greatly reduced by a new generation of assays for intact PTH—two-site, immunoradiometric, or immunochemiluminescence assays—that are now widely available. These use two antibodies directed towards epitopes on either end of the PTH molecule so that only intact, biologically active PTH is measured. They do not detect a cross-reacting substance in malignancy and are sensitive and specific enough to show that PTH is suppressed to subnormal levels in malignancy, as expected.[32,96] Thus, a normal or elevated level of intact PTH in a patient with cancer strongly suggests hyperparathyroidism. Although a few PTH-secreting nonparathyroid tumors have been reported as a cause of hypercalcemia, they are rare and often have unusual histologic features (such as small-cell carcinoma).[97-99]

Treatment of Hypercalcemia

Several recent reviews on the treatment of hypercalcemia are available.[100,101] The mainstay of the initial therapy for hypercalcemia is saline diuresis to reverse the dehydration induced by hypercalcemia and to increase urinary calcium excretion. Calcitonin is a useful adjunct to the initial phase of therapy, as it is nontoxic and acts within 12 to 24 hours. Corticosteroids and combination chemotherapy are sometimes of use in hematologic malignancy or breast carcinoma. Long-term therapy for hypercalcemia in solid tumors is not fully satisfactory. Steroids are usually ineffective. Plicamycin (mithramycin) is efficacious but has significant bone marrow, liver, and renal toxicity.

The introduction of the bisphosphonates—also known as diphosphonates—holds considerable promise for the treatment of hypercalcemia. These agents are pyrophosphate analogues that bind to hydroxyapatite crystals in bone and inhibit the osteoclast directly. The only bisphosphonate currently available in the United States is etidronate disodium.[102] About two thirds of patients respond to a standard course of intravenous therapy (7.5 mg per kg a day for three to five days), and the duration of the response ranges from one to six weeks. Etidronate is relatively nontoxic. Oral etidronate is ineffective as primary therapy for hypercalcemia, although it is used for the treatment of Paget's disease and may prolong the duration of responses to intravenous etidronate.[103] Currently in clinical trials in the US are two more potent and effective drugs, pamidronate (aminohydroxypropylidene bisphosphonate) and alendronate (aminohydroxybutylidene bisphosphonate).[104-106] In an extensive European experience, pamidronate is effective as a single intravenous dose or orally in about 90% of patients with hypercalcemia.[107-109]

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The Biology and Physiology of Aging

Discussant
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This discussion was selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from a transcription, it has been edited by Homer A. Boushey, MD, Professor of Medicine, and Nathan M. Bass, MD, PhD, Associate Professor of Medicine, under the direction of Lloyd H. Smith, Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine.

FLOYD C. RECTOR, MD*: *This conference is given by Itamar Abrass, MD, Head of the Division of Gerontology and Geriatric Medicine at the University of Washington School of Medicine. Dr Abrass, who is a graduate of the University of California, San Francisco, will discuss a topic of substantial relevance to the increasing average age of the patient population: the biologic and physiologic changes of aging.*

ITAMAR B. ABRASS, MD†: The demographic imperative suggests that medical practice in the future will involve a great deal of geriatrics. Older adults presently represent more than a third of patients seen by primary care physicians; this will reach more than 50% in the next century.[1] The number of older persons (aged 65 and older) in this country has grown in both absolute and relative terms. This growth has been influenced by both an increase in the mean life span and a decrease in the birth rate. The group older than 75 years has become even larger. The result is a greater demand on the health care system.

The gain in survival includes both active and dependent years. As the mean life span has lengthened and the maximal life span has remained essentially unchanged, the concept of the compression of morbidity—that is, that the time of dependency will decrease as the life expectancy increases—has been popularized. Unfortunately, at least so far, the data do not support such an outcome. If anything, the mean prevalence of disability seems to be getting worse with time. These data appear in contrast to the clinical impression that older adults are generally healthier and more active. In fact, there may be a bimodal distribution, with some persons getting healthier and others more disabled owing to survival with an illness or disability that was previously fatal.[1] It will be important to define the factors that lead to "successful" aging. Delivering the needed health care and decreasing the time of disability present challenges to both clinicians and scientists.

With aging, two phenomena occur: There is a physiologic decline and an increase in the prevalence of disease. Although these processes influence each other, physiologic decline does occur independent of disease.

In healthy older adults, many physiologic functions are maintained in the basal resting state, but decrements are seen in most organ systems and homeostatic mechanisms when these systems are challenged or stressed. These biologic and physiologic changes of aging were recently reviewed.[2] With advanced age, acute illness is often replaced by chronic disease of multifactorial etiology. Mortality curves are exponential after age 30, with cardiovascular and neoplastic diseases being the commonest causes of death. Yet even in the most elderly persons, apart from the prevalence of disease, the interaction of disease and physiologic change remains important. Pathologists may identify many lesions without defining the cause of death. In fact, the cause of death may have been a relatively minor perturbation of homeostatic mechanisms.

The Biologic Basis of Aging

The importance of genetics in the regulation of biologic aging is shown by the characteristic longevity of each animal species. Several theories of aging have been promulgated. These theories, which have been extensively reviewed by Goldstein and co-workers,[3-5] fall into two general categories: the accumulation of damage to informational molecules, and the regulation of specific genes.

Deoxyribonucleic acid undergoes continuous change in response to both exogenous agents and intrinsic processes. Stability is maintained by the double-strandedness of DNA and by specific repair enzymes. It has been proposed that somatic mutagenesis, due to either a greater susceptibility to mutagenesis or deficits in repair mechanisms, is a factor in biologic aging. In fact, there is a positive correlation of species longevity with DNA repair enzymes. In humans, though, the spontaneous mutagenesis rate is not adequate to account for the number of changes that would be necessary to cause aging, and there is no evidence that a failure in repair systems underlies this phenomenon.

A related theory, the error-catastrophe theory, proposes that errors occur in DNA, RNA, and protein synthesis, each augmenting the others and finally culminating in an error catastrophe. Translation was considered the most likely source of age-dependent errors because it was the final common pathway. But increased translational errors have not been found during aging either in vivo or in vitro. Amino acid substitutions do not increase with aging, although some enzyme activities may be altered by changes in posttranslational modification, such as glycosylation.

The major by-products of oxidative metabolism include superoxide radicals, which can react with DNA, RNA, proteins, and lipids and lead to cellular damage and aging.

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(Abrass IB: The biology and physiology of aging. West J Med 1990 Dec; 153:641-645)

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ABBREVIATIONS USED IN TEXT

HDL = high-density lipoprotein
IL-2 = interleukin-2
LDL = low-density lipoprotein

Several scavenging enzymes and some small molecules, such as vitamin C and vitamin E, protect the cell from oxidative damage. In aging, there is no notable loss of scavenging enzymes, and vitamins C and E do not increase longevity in animals.

At present, the most favored concept of aging is that it is regulated by specific genes. Support for such a hypothesis has been gained mostly from in vitro models of aging. Adult cells can be placed into three categories based on their replicative capacity: continuously replicating, replicating in response to a challenge, and nonreplicating. For example, epidermal, gastrointestinal, and hematopoietic cells are continuously renewed; the liver can regenerate in response to injury; neurons and cardiac and skeletal muscle do not regenerate. In vitro replication is closely related to in vivo proliferation. Neurons and čardiac myocytes from adults can be maintained in culture but do not divide, whereas hepatocytes, marrow cells, endothelial cells, and fibroblasts replicate in vitro. Because they are easily obtained from skin, fibroblasts have been the most extensively studied. Although some cells continuously replicate in vivo, they have a finite replicative life.[6] For fibroblasts in vitro, this is about 50 doublings. The replicative life of fibroblasts in vitro correlates with the age of the donor: the older the donor, the fewer the doublings in vitro. With time in culture, doubling time increases and replication eventually stops.

When fibroblasts from younger donors are fused with nonreplicating senescent cells, DNA synthesis is inhibited in both nuclei. When protein synthesis is transiently inhibited immediately after fusion, DNA synthesis is increased in both nuclei, suggesting that a cytoplasmic protein factor may be involved in inhibiting replication. When senescent cytoplasts—cells without nuclei—are fused with young, dividing cells, DNA synthesis is depressed. Growth arrest both in vivo and in vitro has now been associated with the appearance of a specific protein that may be involved in DNA replication.

These experiments help us understand the finite life span of cells in vitro but do not themselves explain the process of aging in vivo, since organisms do not suddenly die because all their cells stop replicating and die. Nevertheless, factors associated with finite cell replication may have a direct influence on the aging of an organism. For example, fibroblasts aged in vitro or obtained from older adult donors are less sensitive to many growth factors. Such changes may be mediated at both the receptor and postreceptor level. A decrease in the output of growth factors, changes in cell sensitivity to growth factors, or a slowing of the cell cycle may all contribute to impaired wound healing and thus place older persons at greater risk for infection.

For tissues with nonreplicating cells, cell loss may lead to a permanent deficit. With aging, dopaminergic neurons are lost, and this loss influences gait, balance, and the susceptibility to drug side effects. With further decrements due to ischemia or viral infection, Parkinson's disease may develop. Similar cell loss, functional deficits, or both may occur in other neurotransmitter systems and lead to autonomic dysfunction and to an alteration in mental function and neuroendocrine control.

The immune system shows similar age-dependent phenomena. Lymphocytes from older adults have a diminished proliferative response to numerous mitogens. This appears to be due to both a decrease in lymphokines and a lessened response to extracellular signals. As the thymus involutes after puberty, thymic hormone (thymosin) levels decrease. Basal and stimulated interleukin-2 (IL-2) production—and IL-2 responsiveness—also diminishes with age. Diminished IL-2 responsiveness appears to be attributable, at least in part, to a decreased expression of IL-2 receptors. Some immune functions can be restored by adding these hormones or mediators to lymphocytes in vitro, or in vivo by administering them to aged animals. The proliferative defect can also be reversed in vitro by calcium inophores and activators of protein kinase C, suggesting that the T-cell defect may be in the transduction of extracellular signals to intracellular responses.

In vivo, molecular mechanisms such as those described contribute to physiologic deficits and altered homeostatic mechanisms that predispose older persons to dysfunction in the face of stress and disease.[7,8]

The Physiologic Changes of Aging

In assessing data on physiologic function with aging, several factors should be considered[9]: First, in healthy older adults, decrements in function are usually seen only under stress. Further, data generally represent means; with aging, there is usually a greater intragroup variability. Finally, most data are cross-sectional rather than longitudinal. It is also important to determine how the health status of healthy persons was defined.

Cardiovascular

An earlier study suggested that cardiac output at rest declines progressively from about age 20 to age 90.[10] The subjects in this study, however, had not been screened for occult coronary artery disease. The data are different when the population is first screened by stress thallium imaging to exclude subjects with occult coronary artery disease.[11] In this population, the resting cardiac output is unaffected by age from the third through the eighth decades. Cardiac output is also unchanged with age during graded exercise. But with aging, the heart rate decreases and end-diastolic and end-systolic volumes increase. Thus in older subjects, cardiac output during exercise is maintained by using the Frank-Starling mechanism. It seems that even healthy older persons have reserve mechanisms to maintain cardiac output and may therefore be more vulnerable to decompensation when disease is superimposed (Table 1).

These data are also consistent with the notion that myocardial β-adrenergic responsiveness decreases with age. Such changes have been shown in both humans and animals. Heart rate response to isoproterenol infusion decreases with age, and in animals, myocardial contractility decreases as well. This deficit has been shown to be specifically related to β-adrenergic mechanisms and not to intrinsic contractile abnormalities. Basal and stimulated norepinephrine levels increase with age. It is not known whether the deficit in β-adrenergic responsiveness is due to desensitization by endogenous catecholamines or to other age-related phenomena.

Diastolic dysfunction also occurs with aging, with less early diastolic filling and greater dependence on atrial contraction. Such changes may make the elderly more vulnerable to the development of congestive heart failure, particularly in patients with atrial fibrillation. Although elderly

master athletes appear to have less diastolic dysfunction than their sedentary counterparts, preliminary data showed no reversal of existing diastolic dysfunction in elderly subjects who enrolled in an exercise program.

Older persons also show decreased baroreceptor reflex sensitivity—that is, cardiovascular responses to changes in intravascular volume are altered. Such changes may put older patients at a greater risk for inappropriate volume expansion and may also contribute to the higher prevalence of orthostatic hypotension in older adults.

Pulmonary

Except for residual volume, which increases, most pulmonary volumes are unaltered in healthy nonsmoking older adults (Table 2).[12] Compliance increases, however, as the elasticity of structures decreases. The number of supporting structures for small airways also decreases. These changes in small airways lead to an increase in closing volumes such that by the mean age of 65 years, not all the airways are opened during regular breathing in a sitting position.[13] In recumbency, these airway changes occur at age 45. Thus, atelectasis and potentially a complicating pneumonia are more likely to develop in older patients—particularly when lying in bed for prolonged periods—than in younger persons.

Endocrine

The aging process is associated with the development of glucose intolerance (Table 3).[14] The primary defect seems to be one of insulin resistance; most studies show increased insulin levels. Dysregulation of insulin secretion may also be a factor in that the insulin levels may not be appropriate for the level of hyperglycemia. The cause of this impaired carbohydrate metabolism has not been fully determined. Although obesity, activity, and dietary composition influence carbohydrate metabolism, they are not the sole factors in the derangement associated with aging. At the tissue level, the insulin resistance of aging appears to be a postreceptor defect. Insulin receptor number and affinity, as measured on monocytes and adipose tissue, are unaltered with age.[15,16] The postreceptor site that is affected by age is not yet known.

Although the glucose intolerance of aging is not, strictly speaking, diabetes mellitus, it may nevertheless have important health consequences. In healthy older adults, fasting blood glucose levels remain in the normal range, but glycosylated hemoglobin levels rise.[17] Similar changes may occur in other structural proteins and enzymes to an extent that may modify their function. Insulin therapy has been shown to be an independent risk factor for atherosclerosis, and hyperinsulinemia may be a contributory factor to the prevalence of vascular disease in older adults. Even within the normal range of an oral glucose tolerance test, those having blood glucose levels at the upper range have an increased risk of coronary artery disease when compared with those with low-normal levels.

The metabolic clearance rate of thyroid hormone decreases with age.[18] With an intact hypothalamic-pituitary-thyroid axis, thyroxine levels are maintained in the normal range. Yet, with thyroid disease, when exogenous thyroxine is administered, the replacement dose must be adjusted downward to account for the change in clearance.

The most pronounced endocrine change occurs with decreased estrogen production in women during menopause. Along with the changes in reproductive tissues, there is a notable alteration in bone metabolism and, in those with other risk factors, the development of osteoporosis.

An interesting point of debate in the field of aging is the hypothesis that the sex difference in longevity is mediated by the sex difference in atherogenesis, which in turn is mediated by the sex difference in lipoprotein metabolism, and that this, in turn, is determined by gender-specific sex hormone levels.[19] During adolescence, low-density lipoprotein (LDL) levels rise and high-density lipoprotein (HDL) levels decline more in boys than in girls. At menopause, LDL levels rise in women, exceeding those in men throughout the postmenopausal period. If the LDL:HDL ratio is used as the index of atherogenic risk, the sex difference in this ratio can account for a substantial proportion of the sex difference in atherosclerosis and, thus, for a major part of the sex difference in human longevity. The high male-to-female ratio of coronary artery disease mortality progressively decreases after menopause. Although not all studies agree in their findings, several have shown a reduction in coronary artery disease incidence and in all-cause mortality in women using postmenopausal estrogens. These benefits may be mediated by the effects of estrogens on lipoprotein metabolism. Although suggestive, these studies do not directly confirm the hypothesis that relates the influence of endogenous steroids to the sex difference in longevity.

Sex hormone levels do not sharply decline in men as they do during menopause in women, but most studies have

TABLE 1.—*Characteristics of Cardiac Function in Aging*

- Cardiac output during exercise achieved by
  - Lower heart rate
  - Higher end-diastolic volume
  - Higher stroke volume
  - Reliance on Frank-Starling mechanism
- Decreased cardiovascular catecholamine responsiveness
- Diastolic dysfunction
- Diminished myocardial contractile reserve
- Risk for functional compromise

TABLE 2.—*Pulmonary Function in Aging*

- Increase in residual volume
- Decreased elasticity of structures
- Increased compliance
- Decreased number of airway-supporting structures
- Increase in closing volumes
- Increased risk for atelectasis

TABLE 3.—*Carbohydrate Metabolism in Aging*

- Glucose intolerance is common
- Primary defect is insulin resistance
- Dysregulation of insulin secretion
- Insulin receptor number and affinity unaltered
- Postreceptor defect present
- Possible increased risk for vascular disease

TABLE 4.—*Fluid and Electrolyte Homeostasis in Aging*

- Response to sodium restriction blunted
- Less able to excrete solute load
- Increased risk for hyperkalemia
- Water conservation and urine concentration ability impaired
- Increased osmoreceptor sensitivity and propensity for inappropriate antidiuretic secretion syndrome

shown a progressive fall in testosterone levels with aging. In most men the levels do not decrease into the hypogonadal range. Although sexual activity declines with age, this does not seem directly related to testosterone levels. We are not sure yet what effects diminishing testosterone levels have on other metabolic variables. Muscle mass and strength decline with age. How testosterone may contribute to this change has not been assessed. Future studies will need to address this issue as well as the influence of androgens on the hematopoietic system, lipoprotein metabolism, and the general well-being of older men.

Fluid and Electrolytes

Under normal circumstances there are no changes in serum sodium, potassium, hydrogen ion concentration, or vascular volume with age (Table 4). Adaptive mechanisms are nonetheless impaired, and acute illness is often complicated by derangements in fluid and electrolytes balance. The response to sodium restriction is blunted. Older adults can reach sodium balance with restriction, but the response is sluggish, and before balance is achieved, the sodium deficit is greater than in younger persons. Several factors contribute to this salt-losing tendency: With aging, there is nephron loss and a consequent increased osmotic load per nephron. Renin levels are decreased both in the basal and stimulated state. As a result of the changes in renin, aldosterone levels are decreased.

With or without preexisting myocardial disease, older adults are at increased risk for volume expansion. They are less able to excrete an elevated salt load, requiring a longer time to reestablish balance. These changes relate to a decrease in glomerular filtration rate and decreased baroreceptor reflex sensitivity. Potassium handling is also altered with age, and older adults are at increased risk for hyperkalemia. With both the glomerular filtration rate and aldosterone levels decreased, renal potassium excretion is altered. Insulin and catecholamines modulate potassium transport into cells. With decreased insulin and β-adrenergic responsiveness, these adaptive mechanisms are also diminished.

Dehydration is a problem in the elderly especially when fluid intake is limited and insensible loss is increased. Water conservation and urine-concentrating abilities are impaired with aging. Thirst mechanisms are also blunted, compromising the adaptive response to dehydration. These changes, combined with the salt-losing tendency of older persons, help explain why hypertonic volume depletion is such a common presentation.

Possibly the most serious and least well-recognized problem resulting from fluid and electrolyte imbalance in older adults is water intoxication. Again, changes in physiologic variables contribute to this disorder. Basal vasopressin levels are unaltered during normal aging, but infusing a hypertonic saline solution leads to an increase in plasma vasopressin levels that is greater than in younger persons.[20] Conversely, infusing an alcohol solution leads to a diminished suppression of vasopressin in elderly persons.[21] These data suggest increased osmoreceptor sensitivity in older adults with a higher "set point" for vasopressin secretion. Thus certain drugs and pulmonary and central nervous system disorders are more likely to precipitate the syndrome of inappropriate antidiuretic hormone secretion in older patients.

Renal

In cross-sectional studies, renal blood flow, glomerular filtration rate, and creatinine clearance levels have been shown to decrease with age. Creatinine production also diminishes, so that the serum creatinine level may not directly reflect creatinine clearance. It is important to recognize these changes and to make appropriate adjustments in the doses of drugs that are excreted primarily by the kidneys.[22] More recent longitudinal data suggest that renal function does not deteriorate in everyone with aging; in some it remains relatively unchanged, in others it deteriorates only slightly, and in still others there is a more substantial decline.[23] These differences only confirm the variability of aging; nevertheless, the decrease in renal function still must be considered, particularly in those who come under the care of a physician.

Vision and Hearing

Although easily overlooked, age-associated physiologic and functional changes in vision and hearing may contribute to significant dysfunction in older adults. Visual acuity may decrease because of changes in the retina or neural elements. Changes in refractive power lead to both increased hyperopia and myopia. A loss of accommodation leads to hyperopia, and nuclear sclerosis leads to increased lenticular refractive power and myopia. Diminished tear secretion in many older persons, especially postmenopausal women, may lead to dryness of the eyes, which can cause irritation and discomfort. This condition may endanger the integrity of the corneal surface.

Hearing changes do not occur only in the peripheral auditory system.[24] A loss of hearing of pure tones, particularly in higher frequencies—more pronounced in men—can interfere with both hearing and understanding speech. Brain-stem changes may lead to difficulty hearing and localizing sounds in noisy environments. Cortical changes may lead to problems with difficult speech and language. Thus, the changes in hearing function are much more complex than just pure tone loss.

Conclusion

With changes in the environment, mean life span has increased and is approaching that predicted by "ideal" survival curves. Maximal life span, about 120 years for humans, appears not to be changing. Newer cell biology and molecular biology techniques will almost certainly define the genetic factors that determine maximal life span. Prospects for prolonging maximal life span are currently unrealistic, though.

The molecular changes that seem to determine species longevity are most likely also associated with determinants of cellular function. In vivo, these molecular and cellular changes lead to less effective homeostatic mechanisms, increasing an organism's vulnerability to its environment. Understanding these molecular and cellular changes and the environmental influences on them should lead to interventions that increase the mean life span and, more important, decrease disability.

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RURAL ROUTE

The box beside the orange road
Waits for letters no one sends,
Through winter summer winter
Some fifteen odd or so
Passing themselves away
One into the other
Counted only by the date adding itself
To the last X on the calendar
That times the tiny pill or
Red elixir pumping life
Into a wasting frame.

On days the postman brakes, and reaches
Opening the flop-down door,
An old man picks his footing along
The rutted path, pulls forth
A catalog, a water bill or
Some group's plea
To care for starving children.
The old man turns and
Drags his feet
Back up the rutted path.
What can he tell the woman
Behind the window, waiting.

HELEN BRYAN
Washington, DC

Epitomes

Important Advances in Clinical Medicine

Pediatrics

The Scientific Board of the California Medical Association presents the following inventory of items of progress in pediatrics. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, or scholars to stay abreast of these items of progress in pediatrics that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Pediatrics of the California Medical Association, and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
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Diagnosis, Treatment, and Follow-up of Newborns Addicted to Cocaine

THE DIAGNOSIS OF cocaine exposure in infants is fraught with problems. There is little warning of the birth of an addicted neonate because many women using cocaine receive little or no prenatal care and therefore do not come to the attention of medical professionals until the time of delivery. Although comprehensive, nonjudgmental history taking may identify chemical use, a considerable number of women deny use even when they know they will be screened. Testing itself may not give accurate results because the criteria for selecting persons to be screened vary and because cocaine can be detected in the urine for only a short time.

Universal screening has been studied in two settings. Women obtaining prenatal care who were screened for alcohol, opiates, cocaine, and cannabinoids had a 14.8% prevalence rate. There were no significant differences in overall drug detection between public and private clinics or between African-American and white women, although the frequency of cocaine detection was higher in public clinics and in African-American women. Of greatest concern was the difference found in the rates of reporting these results to health authorities after delivery. African-American women were ten times more likely than white women to be reported, and poor women were more likely than others to be reported. In another study, all obstetric patients admitted to an inner-city hospital over a one-year period were screened for opiates, cocaine, and amphetamines. The rate was 20.5%, with cocaine the most frequently found drug (46% of positive screens).

Complications of pregnancy and delivery associated with cocaine use are similar to those associated with smoking and poor prenatal care and nutrition. These may include abruptio placentae, premature delivery, and intrauterine growth retardation. In fact, most infants with exposure to cocaine have also had exposure to cigarettes and other potentially harmful drugs, such as alcohol and marijuana. Often cocaine is used in combination with opiates, and affected infants may show signs of narcotic withdrawal. A close examination for evidence of rare malformations or ischemic damage to the heart, kidneys, intestinal tract, and central nervous system, along with supportive care, is usually sufficient for the majority of infants with cocaine exposure. In addition, the possibility must always be considered that a cocaine-exposed infant has also had exposure to sexually transmitted diseases, including hepatitis B, syphilis, gonorrhea, cytomegalovirus, and human immunodeficiency virus. Controversy exists regarding the increased risk for the sudden infant death syndrome in infants with cocaine exposure, and recommendations for home apnea monitoring are not uniform.

The long-term follow-up of these infants is essential. Neurobehavioral changes usually occur within the first several days of life and may persist throughout the first year. These include irritability, sleep disturbances, hypertonia, and feeding difficulties. Close follow-up for developmental and behavioral disturbances is warranted through school entry because problems with language development, motor skills, attention span, organizational strategies, and interpersonal interactions have been described. The outcome for these infants as they reach their teens and adulthood is unknown but should be of concern to the medical profession and society as a whole.

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Flexible Fiberoptic Bronchoscopy in Children

FLEXIBLE FIBEROPTIC laryngoscopy and bronchoscopy have become useful techniques in evaluating respiratory disease in infants or children. Both procedures can be done on an outpatient basis. The first instrument developed for pediatric use was the 3.5-mm tip-diameter instrument. This bronchoscope contains a channel for the instillation of topical anesthetics or saline solution and the aspiration of lower airway specimens. It can be passed through the nose of most infants and is appropriate for most pediatric procedures. A small 2.7-mm instrument is particularly well suited to infant laryngoscopy and bronchoscopy but does not contain a suction channel. Topical anesthesia is pro-

vided by instillation into the nares of 1% lidocaine and by administering 1% lidocaine onto the larynx and vocal cords, trachea, and lower airway through the bronchoscope channel. A narcotic such as meperidine or fentanyl and midazolam, provided in carefully titrated doses, may also be used. Skill in airway management and respiratory support is required, and monitoring and an environment conducive to ongoing assessment and intervention are essential.

In the outpatient setting, flexible bronchoscopy is commonly done to evaluate airway anatomy. Laryngomalacia, the most common finding in infants with stridor, is easily demonstrated by the dynamic view of the larynx provided by the fiberoptic endoscope. Unilateral or bilateral cord dysfunction, glottic hemangiomas, and laryngeal cysts are easily detected by fiberoptic studies. Tracheomalacia is often associated with laryngomalacia and is well visualized after the bronchoscope is passed into the trachea. Vascular compression of the trachea is also easily recognized, as are other malformations in lower airway anatomy. Persistent wheezing in an older child may be an indication for bronchoscopy, especially if there is evidence of localized disease or a low probability of a history of foreign body aspiration. Rigid bronchoscopy rather than flexible bronchoscopy is, however, indicated for foreign body removal in children. In addition, rigid bronchoscopy is required for the biopsy of endobronchial lesions and is preferred when difficulty in establishing or maintaining the airway is anticipated.

Laryngoscopy and bronchoscopy are equally useful procedures in children admitted to hospital. Infants with chronic lung disease are at risk for subglottic stenosis and lower airway lesions including endobronchial granulations, bronchial stenosis, tracheomalacia, and bronchomalacia. Optimal treatment can be provided when these conditions are diagnosed. Flexible laryngoscopy can be used in intensive care units to evaluate the upper airway before or during extubation. It is particularly useful in evaluating the resolution of epiglottitis and in evaluating laryngeal injury following prolonged intubation or inhalation injury.

Bronchoscopy and bronchoalveolar lavage have proved to be particularly useful in diagnosing *Pneumocystis carinii* pneumonia in children with human immunodeficiency viral infection. Bronchoalveolar lavage is also useful in the diagnosis of pneumonia in children whose immune system is compromised by chemotherapy or other causes and in the evaluation of chronic radiographic infiltrates in children with chronic lung disease of unknown cause.

Complications of flexible laryngoscopy and bronchoscopy are generally infrequent. Minor complications occur in 2% to 3% and include epistaxis, transient bradycardia, and adverse reactions to anesthetic agents. Major complications, which include infection, pneumothorax, and laryngospasm, occur in about 0.4% of lower airway examinations. Death has been reported but is such an infrequent occurrence that it is rare even in large series.

Further applications and improvements in technique and instrumentation can only be expected as pediatric flexible bronchoscopy enters its second decade.

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Bone Marrow Transplantation for the Treatment of Genetic Disease

BONE MARROW TRANSPLANTATION, the treatment of choice for various genetic diseases, may be efficacious for three categories of these diseases. The first is one in which the defect is expressed in the marrow stem cell, such as in patients with severe combined immunodeficiency disease. This disorder is the result of a congenital defect in lymphocytes in which the chances of surviving beyond 1 to 2 years of age without a bone marrow transplant are virtually zero, whereas 75% to 80% of children will be cured with its use. Until recently, only a relatively small number of these children could benefit from a bone marrow transplant because of the lack of histocompatible donors. With the development of techniques for depleting partially matched parental bone marrow of T cells, however, virtually every child with severe combined immunodeficiency now can be offered a curative bone marrow transplant. Other congenital marrow stem cell defects for which the procedure has been used include β-thalassemia major, Wiskott-Aldrich disease, chronic granulomatous disease, and osteopetrosis.

The second category of genetic disease is one in which the defect is expressed in all tissues but involves mostly the marrow stem cell population. For example, adenosine deaminase deficiency and nucleoside phosphorylase deficiency, both of which result in severe combined immunodeficiency, and glucocerebrosidase deficiency, which results in Gaucher's disease, are disorders that principally involve bone marrow-derived lymphocytes and mononuclear phagocytes, respectively. Bone marrow transplantation with the successful replacement of these hematopoietic cells can significantly ameliorate the manifestations of these disorders.

The third category of genetic diseases for which bone marrow transplantation may be indicated includes those in which the defect is expressed in all tissues and there is substantial systemic disease involving many organs. The rationale for a bone marrow transplant in these patients is dependent on marrow-derived tissue histiocytes including Kupffer and Ito cells in the liver; Langerhans cells in the skin; microglia cells in the central nervous system (CNS); osteoclasts in the bones; and macrophages in the lung, spleen, lymph nodes, tonsils, and peritoneum. These marrow-derived cells of donor origin can repopulate affected organs in the recipient and provide a new source of enzyme activity. The lysosomal storage diseases are in this third category of genetic disease. More than 100 children with various lysosomal storage diseases have received a bone marrow transplant. Nearly half were children with Hurler's mucopolysaccharidosis, an autosomal recessive disorder affecting the enzyme α-L-iduronidase. Clinical manifestations of Hurler's syndrome include CNS deterioration, growth failure, joint disability, organomegaly, myocardial or cardiac valvular disease, upper airway obstruction with sleep apnea, corneal clouding, and hearing loss. Patients usually die within the first decade of life with mental retardation and severe cardiopulmonary disease. Bone marrow transplantation has been successful in lessening many of the manifestations of this disease and substantially altering its natural history. The dysmorphologic facial and body features are ameliorated, joint function is improved, and the cardiopulmonary abnormalities and organomegaly abate. In terms of the CNS disease, hydrocephalus does not progress or, in some patients, does not develop, and in more than half of the patients there has been no further deterioration in mental state. Whether the successful results of

bone marrow transplantation in Hurler's syndrome will be repeated in other lysosomal storage disorders is unknown, and resolving this question will require carefully controlled clinical trials.

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Fetal Surgery

MOST PRENATALLY DIAGNOSED correctable malformations are best managed by appropriate medical and surgical therapy after maternal transport and planned delivery at term. A few simple anatomic abnormalities with predictable developmental consequences may be corrected before birth, however.

Fetal urethral obstruction interferes with the development of the fetal kidneys and lungs. Studies of animals have shown that obstruction produces renal dysplasia and pulmonary hypoplasia due to oligohydramnios, and these often fatal consequences can be ameliorated by decompression before birth. The natural history of fetal urinary tract obstruction has now been well documented by the sonographic follow-up of untreated cases, and selection criteria have been developed based on the ability to predict fetal renal function from fetal urine electrolyte levels and the sonographic appearance of the fetal kidneys. Although most fetuses do not require intervention, a fetus with bilateral hydronephrosis due to urethral obstruction in whom oligohydramnios develops may benefit from either early delivery and postnatal decompression if the lungs are mature or, if the lungs are immature, in utero decompression either by a catheter shunt placed percutaneously under sonographic guidance or by open fetal intervention to create a fetal vesicostomy. Several hundred fetuses have now been treated. It is clear that improvements in selection make it possible to avoid intervention in most cases and that decompression of an obstructed fetal urinary tract can prevent the development of fatal pulmonary hypoplasia.

Most babies born with congenital diaphragmatic hernia die of pulmonary insufficiency despite optimal postnatal care because their lungs are hypoplastic from intrauterine compression by herniated bowel. Despite more optimistic reports from children's referral centers, which see only the patients who survive transport, the mortality for diaphragmatic hernia diagnosed in utero is approximately 80% based on sonographic follow-up of more than 200 cases. There is a wide spectrum of severity, and some mildly affected children do well with conventional treatment. An algorithm for management has been presented that selects severely affected babies on the basis of a dilated stomach in the chest, mediastinal shift by a large volume of herniated viscera, and the development of polyhydramnios. For severe lesions detected before 24 weeks of gestation, repair before birth is possible. Extensive experimental work in fetal lambs and monkeys has shown that repair before birth is physiologically sound, technically feasible, and can be accomplished with safety for the mother and her reproductive capacity. The repair is technically difficult, and the first attempts in human fetuses failed because of an unanticipated problem with herniation of the fetal liver and kinking of the umbilical vein. The technical problems have proved surmountable, however, and several babies are now thriving after successful in utero repair.

Several other simple anatomic problems may be amenable to repair before birth. Although most cystic adenomatoid malformations of the lung can be corrected after birth, fetal hydrops can develop in fetuses, with large lesions causing significant compression of normal lungs and causing them to die in utero, a sequence that may be reversed by removing the abnormal pulmonary tissue. Some fetuses with large sacrococcygeal teratomas have high-output cardiac failure and hydrops and die in utero—again, a sequence that can be reversed only by interrupting the vascular steal either by occluding the vessels to the tumor or removing the tumor before birth. Simple obstructions to intracardiac blood flow may be amenable to fetal intervention, such as a recent attempt to dilate a stenotic aortic valve before birth. Some fetuses with heart block unrelated to anatomic abnormalities with ventricular rates slow enough (< 45 beats per minute) to cause hydrops and fetal death may benefit from electrical pacing in utero. One of the most interesting observations to arise from experimental and now clinical fetal surgery is that the fetus heals without scarring or fibrosis. Unraveling the mechanisms of scarless healing in the fetus may allow therapies that improve healing after birth. Intervention for disfiguring but not life-threatening anomalies such as cleft lip and palate and craniofacial anomalies is not warranted at present, however. Fetal intervention is the logical culmination of advances in fetal diagnosis, and new applications are rapidly evolving.

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Predictors of and New Therapy for Jaundice

IN SICK, PREMATURE, or severely jaundiced infants, the evaluation of risk for brain injury caused by bilirubin should include the measurement of arterial blood gas pressures, albumin level, and total serum bilirubin level. In a term infant with normal arterial pH and without hemolytic disease, the total binding capacity (in milligrams per deciliter) should probably not exceed the albumin concentration (in grams per deciliter) more than seven times. For example, if an infant has an albumin level of 3.4 grams per dl, an exchange transfusion should be done if the bilirubin level reaches 23.8 mg per dl (3.4 × 7). Using Système International (SI) units, the multiple should be 12: 34 grams per liter (albumin) × 12 = 408 μmol per liter (bilirubin). In very sick infants, the quality of albumin binding may be impaired, and a multiple of 5 to 6 times the albumin concentration might yield a more appropriate estimate of risk (9 to 10 × using SI units). Because the tissue deposition increases linearly with the hydrogen ion concentration, aci-

dosis should be aggressively corrected in patients at high risk for bilirubin encephalopathy. This is particularly important in patients with respiratory acidosis because carbon dioxide rapidly equilibrates across the blood-brain barrier and increases the cerebral flow and bilirubin delivery to the brain.

For well, term babies without hemolysis or a serum bilirubin level well above 20 mg per dl, there is remarkably little evidence for adverse effects caused by bilirubin on intelligence quotient, neurologic function, or hearing. In fact, the diagnosis of neonatal jaundice as a "problem" may have negative consequences on maternal behavior and attitudes in the early, crucial months of infant development.

Nonetheless, the effects of hyperbilirubinemia in premature infants, who have an increased bilirubin production compared with term infants, and term infants who have increased bilirubin production because they are sick or have hemolytic disease may be deleterious and different from those in well, term infants. Because a degradation of heme results in the equimolar production of carbon monoxide (CO) and bilirubin, the respiratory CO excretion rate, the end-tidal CO concentration, and the blood carboxyhemoglobin level can be used as indices of bilirubin production. Noninvasive technology currently exists for detecting an excessive production of bilirubin even before the development of jaundice.

Currently the two most widely used treatments for exaggerated neonatal hyperbilirubinemia are phototherapy and exchange transfusion, therapies which remove bilirubin that has already been produced. The suppression of bilirubin formation, however, is a more logical preventive strategy, particularly when reserved for those patients who produce an excessive amount of the pigment. The first and rate-limiting step in the degradation of heme to bilirubin is catalyzed by the microsomal enzyme heme oxygenase. Numerous inhibitors of heme oxygenase have been identified, including tin, zinc, chromium, and manganese porphyrin complexes. Zinc protoporphyrin has recently been shown to inhibit bilirubin production and ameliorate hemolytic jaundice in nonhuman rhesus primates.

Two other pharmacologic strategies for ameliorating neonatal jaundice are also being considered. One involves bilirubin oxidase, a mitochrondrial enzyme that is capable of breaking down bilirubin to biliverdin and has been used in rodents with a congenital deficiency of glucuronyl transferase to interrupt the enterohepatic circulation of bilirubin. Another involves a traditional Chinese herbal concoction called *yin zhi huang,* which has been used in Asia to treat hepatitis and neonatal jaundice and has undergone some recent studies showing that it enhances bilirubin clearance from plasma and increases the conjugation of bilirubin by the liver.

Any new strategies to provide more specific therapies for infants at risk for dangerous neonatal jaundice should be combined with screening programs to identify infants who produce excessive amounts of bilirubin and who are at risk for potentially dangerous jaundice. Thus, infants who are at low risk for potentially dangerous neonatal jaundice could be spared an unnecessary use of laboratory testing and therapies.

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Interventional Catheterization for Congenital Cardiac Defects

HEART DEFECTS ARE the most common serious congenital anomalies. Interventional catheterization has had a major effect on the prognosis and costs of these defects. As many as 20% of structural cardiac defects can now be treated effectively in the cardiac catheterization laboratory, and this percentage could approach 40% in the near future. Therapy without thoracotomy, transfusion, or even an overnight stay in a hospital is now possible.

The list of potential uses of balloon valvuloplasty or angioplasty techniques is long and includes valvar and arterial pulmonic stenosis, aortic stenosis, coarctation, rheumatic mitral stenosis, and postoperative stenotic lesions. The greatest success and effect to date has been with valvar pulmonic stenosis. More than 800 balloon pulmonary valvuloplasties have been reported to an international registry. The transvalvar gradient was reduced greater than 70% with a mortality rate of 0.2%. The procedure was less effective in patients with a dysplastic pulmonary valve as is seen in Noonan's syndrome.

Survival rates and gradient reduction for balloon pulmonary valvuloplasty in infants with critical pulmonic stenosis have exceeded those of surgical valvotomy. Cyanotic heart defects with restricted pulmonary blood flow can also be palliated by balloon pulmonary valvotomy, obviating the need and problems associated with a Blalock-Taussig shunt or its variants. Many other stenotic lesions can be dilated, with current results approximating those of surgical outcome, but at lower cost financially and emotionally. The risks of restenosis of dilated arterial segments can be diminished with the use of intravascular stents.

Interventional procedures place great demands on the catheterization team and require experience and coordination. Complications may occur with valvuloplasty, including blood loss, obstruction of femoral vessels, vessel rupture, perforation, and valve destruction with insufficiency. The largest reported complication rate is about 12%, of which half were considered major. The incidence of complications is inversely related to a patient's age. Most complications occur in the very young where the necessity for operator experience and appropriate equipment size is the greatest. In some series, femoral vessel obstruction may occur in as many as 10% of angioplasty-treated children but usually can be treated medically. The overall mortality rate is, however, low (about 0.7%). Because of the potential serious complications, a surgical team should be available to minimize mortality. The economic effects of angioplasty-valvuloplasty procedures can be substantial with most interventional catheterizations costing 20% to 50% of a comparable operative procedure.

Catheter techniques to occlude pathologic or postoperative cardiac or great vessel communications have also become well established. Metallic coils or detachable balloons can be used to permanently occlude systemic-to-pulmonary

artery collaterals, residual aorticopulmonary shunts, persistent left superior venae cavae, and arteriovenous malformations. The current success with patent ductus arteriosus occlusion devices will make their use the treatment of choice for older children with this defect. The demonstrated efficacy of the double umbrella or clamshell occlusion device for atrial septal defect and muscular ventricular septal defect should lead to prompt Food and Drug Administration approval and widespread clinical use. Additional interventional advances are on the horizon and will continue to improve the prospects for a near-normal quality of life for infants born with congenital heart disease. Cost savings will effectively allow for increased access to care within budgetary constraints.

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Diagnosis and Treatment of the Acquired Immunodeficiency Syndrome in Children

THE ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS) in children—symptomatic human immunodeficiency virus (HIV)—is becoming one of our nation's largest health problems; 3,213 cases of AIDS in children, ages 0 to 19, have been reported to the Centers for Disease Control (CDC) as of October 1, 1990. They represent about 2% of the total AIDS cases in the United States, now numbering more than 150,000. Further, there is considerable underreporting of pediatric AIDS because rigid criteria are necessary. It is estimated there may be as many as threefold more unreported pediatric AIDS cases in the US. It will soon be the fifth leading cause of death in children. Indeed, about 2,000 infants with HIV infection will be born to about 5,600 HIV-infected mothers annually in the US. Most of the cases are in the urban areas of populous states such as New York, New Jersey, Florida, Texas, and California.

Nearly all HIV-infected children have acquired their disease perinatally from their HIV-infected mothers. Transfusion-acquired cases make up only 11% of the total reported cases, and nearly all of these patients were infected before April 1985, when the routine testing of blood products commenced. Mothers have become infected because of their own intravenous drug use (51%) or their sexual partner's seropositivity (38%), usually also a result of intravenous drug use. Most of these mothers are members of disadvantaged minorities, particularly African American (51%) or Hispanic (20%). (These groups make up 18% of the total US population.) Thus, pediatric AIDS is now a disease of urban disadvantaged minority populations.

Infants and children with HIV characteristically get sick 6 to 18 months after infection; the first manifestation usually is recurrent respiratory tract infection, particularly bacterial or viral pneumonia. *Pneumocystis carinii* infection, candidiasis, persistent diarrhea, and poor growth are also noted early. Encephalopathy occurs in many children as the illness progresses, leading to intellectual and motor deterioration. Some older children get a characteristic pulmonary disorder, lymphoid interstitial pneumonitis, producing diffuse nodular or reticular pulmonary infiltrates and progressive dyspnea. The cause is not known.

A physical examination may reveal prominent lymphadenopathy and hepatosplenomegaly. Parotitis may also be present. Other features such as growth failure are nonspecific. Immunologic abnormalities in HIV-infected infants and children include hypergammaglobulinemia; diminished antibody responses, CD4 cell (T-helper) depletion; reversal of the CD4 to CD8 (T-helper:T-suppressor) ratio; and poor results on functional tests of cellular immunity, such as proliferative responses to mitogens.

Table 1 suggests which infants and children may have HIV infection and should have an HIV-antibody test. A positive HIV-antibody test by screening enzyme-linked immunosorbent assay and confirmatory Western blot test generally indicates HIV infection in children older than 15 months.

Diagnosing HIV disease by antibody testing in infants is complicated by the presence of transplacental maternal HIV antibody in infants' circulation until as old as 15 months. The best way to establish a diagnosis in these infants is to identify HIV by culture of a patient's lymphocytes. The presence of HIV antigen (p24) in the plasma also is diagnostic, but it often is not present in early illness. The polymerase chain reaction to detect viral DNA promises to be a sensitive and specific test, but it is not routinely available.

Treatment is now available that will prolong life and prevent opportunistic infection in children with AIDS. *P carinii* pneumonia prophylaxis with the combination drug trimethoprim and sulfamethoxazole is recommended for all infants younger than 15 months with established HIV infection regardless of immunologic state, any older HIV-positive child with a CD4 lymphocyte count of less than 0.4×10^9 per liter (400 cells per μl), and any HIV-positive child with a previous *P carinii* infection. Trimethoprim-sulfamethoxazole is given as Bactrim or Septra, 150 mg per m^2 a day of the trimethoprim component, in two divided doses three times a week (Monday, Tuesday, and Wednesday).

The use of zidovudine (AZT) is recommended for chil-

TABLE 1.—*Indications for Testing for Human Immunodeficiency Virus (HIV) in Children and Adolescents*

Who could be tested
Children of HIV-infected parents
Children of "high-risk" parents—IV drug users, prostitutes, bisexuals, past residents of countries where HIV is endemic
Children transfused between 1978 and April 1985, before HIV testing
Children transfused after April 1985 in whom clinical or laboratory features of immunodeficiency develop
Children with hemophilia who received clotting factor concentrates between 1978 and January 1985, before heat treatment
Children whose parents request testing
Who should be tested
Children with opportunistic infections suggestive of an immunodeficiency
Children with evidence of T-cell immunodeficiency
Children with recurrent infections and hypergammaglobulinemia (IgG plus IgM plus IgA levels > 18 grams per liter [> 1,800 mg per dl])
Children with unexplained myopathy, nephritis, hepatitis, or progressive neurologic disease
Children who are bone marrow or organ donors
Children at "high risk" due to IV drug use, prostitution, or sex with high-risk persons

Ig = immunoglobulin, IV = intravenous

dren with CD4 counts of less than 0.5×10^9 per liter (500 cells per μl) or any child with CDC-defined AIDS. The usual initial dose is 180 mg per m^2 per dose every six hours, with dose reductions as needed because of hematologic or hepatic toxicities. Zidovudine is particularly valuable in reversing HIV encephalopathy. Side effects include neutropenia, anemia, and hepatic derangement.

The intravenous administration of immune globulin, 400 mg per kg every three to four weeks, is recommended if there is evidence of poor antibody function. All routine childhood immunizations should be given except that inactivated polio vaccine is given rather than oral polio vaccine. Despite these immunizations, immunity is not assured owing to deficient antibody responses. Appropriate antibiotics and antivirals are used promptly with each significant infection. Varicella-zoster immune globulin is used following varicella exposure. Other drugs such as dideoxyinosine (DDI), soluble CD4, and hyperimmune intravenous immune globulin are under investigation. The use of these therapies should improve survival, which is now about 38 months from time of diagnosis.

California has three centers for the treatment of pediatric AIDS: the San Francisco Bay Area (D. Wara, MD [415] 476-1736), the Los Angeles area (Y. Bryson, MD [213] 206-6369), and the San Diego area (S. Spector, MD [619] 543-6447). All are part of a national network of pediatric AIDS centers supported by the National Institutes of Health. Further information and referrals are available at these centers.

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Newborn Hemoglobinopathy Screening

In February of 1990, California implemented hemoglobinopathy screening as part of the routine neonatal screening program. The hemoglobinopathy screening is done on all newborns regardless of race, creed, color, or ethnicity. The purpose of the screening is to identify infants with a clinically significant hemoglobinopathy and refer them to comprehensive-care sickle cell centers for follow-up support services. The Cooperative Study of Sickle Cell Disease, conducted by the Sickle Cell Branch of the National Institutes of Health, showed the effectiveness of parental education for the pediatric patients. Most deaths of children with sickle cell disease occurred between the ages of 1 and 3 years from serious infections. It has been reported that educating parents to take a temperature and identify a fever has decreased the mortality rate of young children with sickle cell anemia. Furthermore, the education of and counseling to parents on the importance of prophylactic penicillin have been demonstrated in national studies to decrease significantly the morbidity and mortality due to overwhelming infection or sepsis in infants with hemoglobin SS disease. Because sickle cell anemia occurs in 1 in 500 live births in the African-American population, primary care providers must be aware of the newborn screening process and participate actively in the referral and follow-up of these patients.

Primary physicians are notified by letter or a telephone call from the newborn screening nurse coordinator in the area. The patient's name, date of birth, mother's name and address, and preliminary diagnosis are provided. When a patient is seen for the initial visit, it is strongly recommended that the primary physician begin prophylactic penicillin therapy, inform the family of the comprehensive care sickle cell center in the area and encourage them to call for an appointment, and call the sickle cell center and make a referral.

The role of comprehensive-care sickle cell centers in the management of clinically significant hemoglobinopathies in newborns includes medical intervention and consultation by a pediatric hematologist with specific training in hemoglobinopathies; a nurse specialist to provide clinical assessment and parental education; a master's level social worker or equivalent family therapist to discuss psychosocial issues or needs that may affect the child or family; and within the comprehensive care setting, other health professionals who are available for consultation from various specialty areas to meet patients' needs.

In addition to identifying sickle cell disease, the newborn screening program will detect variant forms of other significant hemoglobinopathies as well as heterozygote hemoglobin disorders such as AS, AC, and AD. These traits appear to be harmless and do not cause serious health problems. Combination hemoglobinopathy-thalassemia syndromes will also be detected by the newborn screening program. In California, all infants having these traits are referred to primary care physicians by a letter from the Department of Health Services, Newborn Screening Section. This letter also lists the names of sickle cell counseling centers in the family's area that can provide information on the hemoglobin trait the child has by the authorization code assigned by the Newborn Screening Section. The physicians again play an important role in providing initial information and counseling and by referring such families to comprehensive-care sickle cell centers for more in-depth education and counseling.

Full participation by primary care providers in this program is essential for its success and should result in optimal care for children with substantial hemoglobinopathies.

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Steroid Therapy for Bacterial Meningitis

The idea that glucocorticoids might prove to be a useful adjunctive therapy for meningitis has been in the literature for more than 30 years. The choices of experimental design, the choice of steroids administered, the choice of dose, and the lack of clarity about which outcomes to measure all stood in the way of demonstrating a beneficial effect. During the past five years two separate lines of investigation have provided much new information in this area.

The development of an excellent rabbit model for purulent meningitis allowed several groups of investigators to work out the pathophysiologic events in bacterial meningitis. Bacteria enter the central nervous system, multiply rapidly, and liberate cell wall products (endotoxin,

teichoic acid). These inflammatory agents in turn stimulate host cells to produce various potent cytokines (tumor necrosis factor, interleukin, and others). The inflammatory cascade results in a serious pathologic disorder including brain edema, increased intracranial pressure, decreased cerebral perfusion, a loss of autoregulation, and, ultimately, permanent brain damage. Rabbits are well suited to the study of various forms of therapy, including the use of anti-inflammatory drugs. It has been clearly shown that in rabbits the use of dexamethasone given simultaneously or before antimicrobials in cases of *Hemophilus influenzae* meningitis abolishes or greatly ameliorates the profound inflammatory response and other untoward consequences of infection that cause most of the residual damage. Not all steroids have similar anti-inflammatory action. Methylprednisolone, for example, fails in several important respects.

At the same time, the use of dexamethasone has been evaluated in human studies, mostly in children with *H influenzae* meningitis. The pathophysiologic studies had results similar to those found in rabbits. Children given dexamethasone had fewer signs of inflammation. Adverse effects of dexamethasone use appear to be limited to a small incidence (1.5%) of gastrointestinal bleeding. Well-controlled outcome studies in several hundred patients failed to show the effects of dexamethasone therapy on mortality, which was low in this series. The early use of the drug, however, along with antimicrobial therapy was associated with a distinctly lower incidence of bilateral moderate or greater hearing loss compared with results in patients treated with antimicrobials or a placebo. Confounding the results was the use of cefuroxime as the antibiotic in portions of the study. This agent is no longer recommended for the treatment of bacterial meningitis due to its delay in sterilizing the cerebrospinal fluid of patients.

The immediate application of the new knowledge to clinical practice is still somewhat controversial. Multicenter studies including larger numbers of children in the United States and abroad are in progress. Larger numbers will be of great value in further evaluating both the beneficial effects of adding steroids to the treatment regimen and further exploring any adverse effects.

As we await the outcome of these expanded trials, the American Academy of Pediatrics has recommended "individual consideration of dexamethasone for bacterial meningitis in infants and children 2 months of age and older after the physician has weighed benefits and possible risks." The only published regimen for dexamethasone is 0.6 mg per kg of body weight per day in four divided doses given intravenously for four days beginning with or just before the first dose of antibiotic therapy. The use of dexamethasone in bacterial meningitis due to organisms other than *H influenzae* is not established, but it may be reasonable to use the drug in a child with purulent meningitis in whom the bacterial cause is not yet confirmed. There is no reason to use dexamethasone in patients with aseptic meningitis. The use of steroids in adult patients should await the outcome of further clinical trials. Another important area awaiting clinical trials is the use of steroids in neonatal meningitis.

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Alerts, Notices, and Case Reports

McCune-Albright Syndrome

A Case of Primary Hypogonadism Obscured by Hyperprolactinemic Hypogonadotropic Hypogonadism

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In the 50 years since Fuller Albright and his colleagues described a syndrome characterized by "osteitis fibrosa disseminata, areas of pigmentation, and precocious puberty in females,"[1] various case reports and review articles have appeared expanding the endocrinologic dimensions of what has become known as the McCune-Albright syndrome.[2-20] It is now recognized that the syndrome occurs in men as well as women and that the endocrine abnormalities can be manifested as deficiency syndromes and hyperfunctional states. We report the case of a patient with the McCune-Albright syndrome in whom primary gonadal failure was obscured by hypogonadotropic hypogonadism associated with hyperprolactinemia and acromegaly.

Report of a Case

The patient, a 26-year-old man, was the sole product of a nonconsanguineous marriage and a term pregnancy. He had many limb fractures as a child, and a diagnosis of polyostotic fibrous dysplasia was made when he was 5. He underwent the placement of rods in both hips. Puberty began at age 12. Two months before our initial evaluation, a carpal tunnel syndrome developed in his right hand and he noticed a weight gain of 4.5 to 7 kg (10 to 15 lb). There was no change in bowel habits, heat or cold intolerance, or changes in his skin or hair. An episode of nephrolithiasis at age 22 required a lithotomy. The family history was pertinent only for a cousin whose facial features were reportedly similar to those of the patient. He complained of hyposmia and infrequent erections.

On physical examination the patient appeared well developed, virilized, and stocky with leonine facies. He had large pigmented macules with ragged edges on the face, back, and trunk. The thyroid was slightly enlarged and contained a 0.5-cm nodule in the left lobe. There was bilateral Tanner stage II gynecomastia without galactorrhea, a normal-sized circumcised penis, and the testes measured 12 cm^3 bilaterally. The hair distribution was normal for an adult man. He was hyposmic in response to challenge with tobacco, coffee grounds, and tea leaves. The reproductive hormone values were as follows: total testosterone content, 3.85 nmol per liter (normal, 10.4 to 34.7); luteinizing hormone (LH), 6 IU per liter (normal, 4 to 18); follicle-stimulating hormone (FSH), 12 IU per liter (normal, 5 to 20); and prolactin, 120 μg per liter (normal <20). The growth hormone level was 10 μg per liter, and the insulinlike growth factor I-somatomedin C (IGF-I) level was elevated at 519 ng per ml (normal, 40 to 170). A serum growth hormone-releasing hormone level was undetectable. Thyroxine, thyroid-stimulating hormone, iron, and serum iron-binding capacity values were all normal.

Serum growth hormone concentrations did not suppress after a 75-gram glucose challenge, consistent with a diagnosis of acromegaly. There was no gonadotropin response to a 100-μg intravenous challenge of gonadotropin-releasing hormone (GnRH [gonadorelin hydrochloride]).

Radiographs of the legs revealed polyostotic fibrous dysplasia with its characteristic ground-glass appearance. A

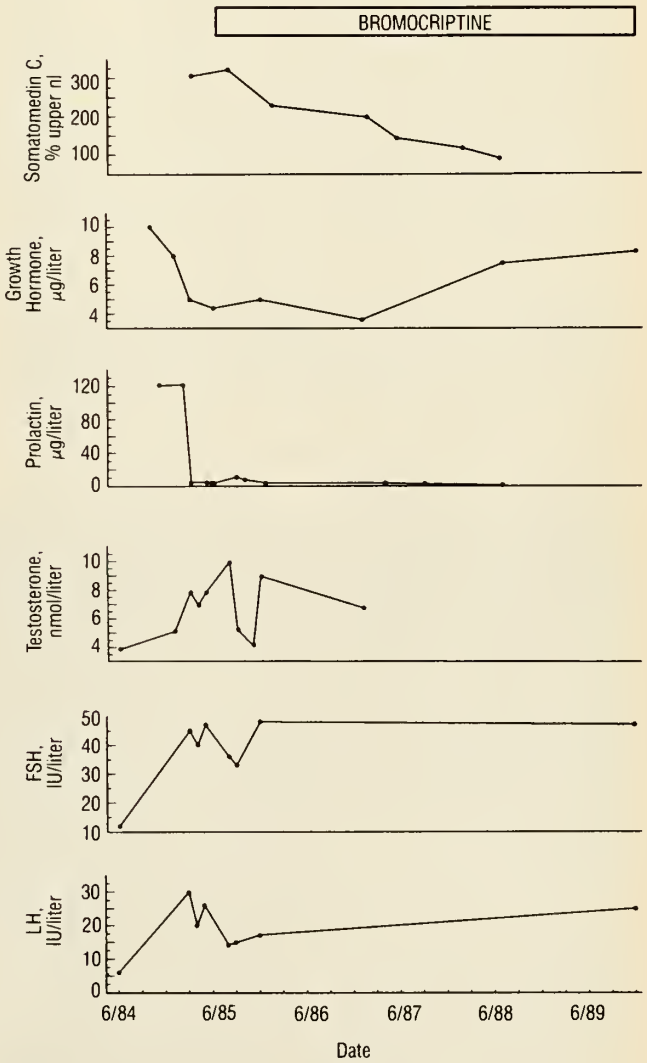

Figure 1.—The clinical response to bromocriptine mesylate therapy is shown. Somatomedin C is expressed as a percentage of the upper limit of normal values; normal values for the other hormones: growth hormone, less than 10 μg per liter; prolactin, less than 20 μg per liter; luteinizing hormone (LH), 4 to 18 IU per liter; follicle-stimulating hormone (FSH), 5 to 20 IU per liter; testosterone, 10.4 to 34.7 nmol per liter. The patient was also receiving testosterone, 300 mg intramuscularly every 3 weeks, between December 1985 and November 1989.

(Swislocki ALM, Camargo CA, Hoffman AR: McCune-Albright syndrome—A case of primary hypogonadism obscured by hyperprolactinemic hypogonadotropic hypogonadism. West J Med 1990 Dec; 153:653-656)

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ABBREVIATIONS USED IN TEXT

FSH = follicle-stimulating hormone
GnRH = gonadotropin-releasing hormone
IGF-I = insulinlike growth factor I
LH = luteinizing hormone

computed tomographic scan of the head showed pronounced thickening of the bones of the skull and sella turcica, without any apparent pituitary tumor or erosion of the sella. No abnormality was noted in the area of the pituitary stalk or hypothalamus.

The diagnosis of McCune-Albright syndrome was made, manifesting as polyostotic fibrous dysplasia, characteristic cutaneous "coast of Maine" pigmented lesions,[3] hyperprolactinemia with hypogonadotropic hypogonadism, acromegaly, and euthyroid multinodular goiter. Because the dense bony lesions in the sella turcica might complicate a transsphenoidal operation and because imaging studies failed to show a pituitary tumor, he was treated with bromocriptine mesylate. The clinical response is shown in Figure 1. With the initiation of bromocriptine therapy, there was a fall in the prolactin level and, eventually, of growth hormone levels, with a rise in both gonadotropin and testosterone values. The patient reported that his sense of well-being and libido increased markedly, and he grew a beard. Although subjective improvement persisted, the testosterone concentration again fell below the normal range; the LH and FSH concentrations rose, the LH level to 30 IU per liter and then stabilizing at 17 IU per liter and the FSH level to 45 IU per liter, stabilizing at 35 to 45 IU per liter, suggesting the diagnosis of primary gonadal failure. The patient is currently receiving bromocriptine (10 mg orally three times a day) and testosterone enanthate (300 mg intramuscularly every three weeks). His most recent IGF-I value is 160 ng per ml, but growth hormone and prolactin levels are both within normal limits at 8.3 μg per liter and 2 μg per liter, respectively.

After about four years on a regimen of bromocriptine and testosterone, the patient's radiographic and endocrinologic studies were repeated. Magnetic resonance imaging revealed a 5-mm microadenoma of the pituitary gland. A GnRH stimulation test was done after testosterone therapy had been discontinued for four weeks: 15 to 45 minutes after 100 μg of GnRH was administered intravenously, the FSH level rose from 47 IU per liter at baseline (normal <20) to 63 to 68 IU per liter, and the LH level rose from 25 IU per liter at baseline (normal <15) to 60 to 69 IU per liter. In view of the microadenoma, a neurosurgical consultation was obtained and a decision was made in consideration of the thick bone in the sellar floor to avoid a neurosurgical approach to the pituitary and to treat the patient with stereotactic external beam irradiation. Treatment is pending at this time.

Discussion

The initial definition of the McCune-Albright syndrome required the triad of pigmented skin lesions, fibrous dysplasia of bone, and precocious puberty in girls.[1] Most of the reported cases subsequently grouped under the heading of the McCune-Albright syndrome have included patients with precocious puberty[1-8,11,13-15,17]; there have also been cases of secondary hypogonadism in both sexes.[13,16,17,20] Acromegaly and gigantism have also been reported numerous times.[13,17,19,21-26] The endocrinopathies reportedly associated with the McCune-Albright syndrome are summarized in Table 1.

The case presented in this report is unusual, however, in that the primary hypogonadism was masked by hyperprolactinemia.[27,28] The elevated gonadotropin levels characteristic of primary gonadal failure were initially suppressed. When prolactin secretion was suppressed by bromocriptine therapy, LH and FSH concentrations were disinhibited and rose towards the castrating range.

The primary hypogonadism reported in this patient appears to be unique in the overall experience with this curious syndrome. In the other cases of the McCune-Albright syndrome in which hypogonadism was reported,[13,16,17,20] data were most consistent with secondary (central) hypo-

TABLE 1.—*Endocrinologic Syndromes in the McCune-Albright Syndrome*

Endocrinopothy	*Reference*
Precocious puberty	
Girls	Albright et al, 1937[1]; Benedict, 1962[2]; Danon et al, 1975[5]; D'Armiento et al, 1983[6]; Foster et al, 1984[7]; Chung et al, 1983[13]; Andrews et al, 1974[15]; Lipson and Hsu, 1981[17]; Geffner et al, 1987[25]
Boys	Benedict, 1962[2]; Benedict, 1966[4]; Lightner et al, 1975[8]; Benjamin and McRoberts, 1973[11]; Nitzan et al, 1973[14]
Enlarged testes with Leydig cell hyperplasia	Benjamin and McRoberts, 1973[11]
Hypogonadism (male)	Joishy and Morrow, 1976[20]
Small testes (without precocious or delayed puberty)	Benedict, 1962[2]
Thyroid nodules	Benedict, 1962[2]; Benjamin and McRoberts, 1973[11]
Hyperthyroidism	Benedict, 1962[2]; D'Armiento et al, 1983[6]; Moldawer and Rabin, 1966[10]; Andrews et al, 1974[15]
Acromegaly, gigantism	Lightner et al, 1975[8]; Nakagawa et al, 1985[9]; Chung et al, 1983[13]; Lipson and Hsu, 1981[17]; Harris, 1985[19]; Joishy and Morrow, 1976[20]; Powell, 1976[21]; Lightner and Winter, 1981[22]; Polychronakos et al, 1982[23]; Cuttler, 1986[24]; Geffner et al, 1987[25]; Pacini et al, 1987[26]
Cushing's syndrome	Danon et al, 1975[5]; Benjamin and McRoberts, 1973[11]
Hyperprolactinemia or galactorrhea	Chung et al, 1983[13]; Harris, 1985[19]; Polychronakos et al, 1982[23]; Cuttler et al, 1986[24]; Pacini et al, 1987[26]
Amenorrhea	
Primary	Shires et al, 1979[16]
Secondary	Chung et al, 1983[13]; Lipson and Hsu, 1981[17]
Non-insulin-dependent diabetes mellitus	Moldawer and Rabin, 1966[10]; Lipson and Hsu, 1981[17]
Hyperplastic parathyroidism (or hyperparathyroidism)	Benedict, 1962[2]; Ehrig and Wilson, 1972[12]
Hypophosphatemia	McArthur et al, 1979[18]
Rickets	McArthur et al, 1979[18]
Gynecomastia	Benjamin and McRoberts, 1973[11]

gonadism. The persistently elevated FSH level, the elevated LH levels following the cessation of testosterone replacement, and the exaggerated gonadotropin response to GnRH administration support the diagnosis of primary hypogonadism and rule out the presence of central or hypogonadotropic hypogonadism.

Primary hypogonadism can be developmental or acquired.[27-29] Developmental causes include Klinefelter's syndrome or its mosaic variants. Klinefelter's syndrome is characterized by a 47,XXY karyotype, and the most common variant is a 46,XY/47,XXY mosaic. These patients typically have small, firm testes, impaired sexual maturation, gynecomastia, underandrogenization, and mild mental deficiency. Although the patient reported here has small, firm testes, he has above-normal intelligence, had a normal puberty, and is well androgenized, making Klinefelter's syndrome or one of its variants unlikely.

A more likely explanation is that this patient's primary hypogonadism is acquired. The major causes include infection, trauma, irradiation, and drugs.[29] Respectively, he has no history of mumps orchitis, trauma, or radiation exposure. The typical drugs associated with testicular suppression include cyproterone, spironolactone, and ethanol. This man drinks socially, but there is no evidence by history of impaired job or personal function and no physical evidence or laboratory data to suggest alcohol abuse. He has never received antineoplastic agents or cimetidine, and he says he does not use marijuana.

Other rarer causes of testicular failure include autoimmune orchitis (usually in the context of multiple autoimmune endocrinopathies) and granulomatous disease—specifically, leprosy.[29] Testicular atrophy develops in about 10% to 20% of persons with leprosy, although this is less common in other forms of systemic granulomatous disease. This patient has no evidence of either autoimmune endocrinopathy or granulomatous disease. Thus, although he does not appear to have a developmental cause of testicular failure, there is no clear evidence leading to a cause of acquired testicular failure.

The means by which hyperprolactinemia induces hypogonadism are not well understood. Carter and co-workers pointed out in their series of hypogonadal men with prolactin-secreting tumors that both the testes and pituitary gland responded appropriately to stimulation by human chorionic gonadotropin and exogenous GnRH, respectively, suggesting that GnRH deficiency was a major causative factor.[30] Prolactin may also interfere with the conversion of testosterone to dihydrotestosterone.[31,32] Zini and colleagues reported that hyperprolactinemic men not only had normal basal LH levels in the presence of lower testosterone concentrations but also a delayed peak response of LH levels to GnRH that partially corrected with the administration of bromocriptine.[33]

The initial finding of hypogonadotropic hypogonadism probably reflects suppression of the hypothalamic-hypophyseal axis with a reduction in hypothalamic GnRH secretion by elevated circulating prolactin levels. With the control of hyperprolactinemia by bromocriptine therapy, gonadotropin secretion initially increased, but serum testosterone levels did not reach the normal range, indicating the presence of primary testicular failure.

The cause of the hyperprolactinemia, as well as the hypersomatotropinemia, is most likely the microadenoma uncovered on the recent magnetic resonance imaging scan. Pituitary tumors may produce both growth hormone and prolactin,[34] and in the absence of immunohistochemical confirmation of the tumor tissue type, we can only speculate that this is the explanation. Alternatively, the tumor is producing growth hormone, and prolactin is being released as a result of the tumor interfering with the normal inhibition of prolactin secretion, although the small size of the tumor makes this less likely. A recent examination of coexistent growth hormone and prolactin hypersecretion in three patients with the McCune-Albright syndrome without pituitary masses on high-resolution imaging suggests that abnormal hypothalamic function with or without a concomitant embryologic defect in pituitary development and activity may underlie the disordered secretion dynamics of growth hormone and prolactin.[35]

The combination of anosmia and hypogonadism is occasionally seen in patients with hypothalamic hypogonadism (Kallmann's syndrome). In our patient, however, the hyposmia was probably due to severe sclerotic cranial bone disease obliterating the cribriform plate of the ethmoid and destroying the olfactory filaments.

The great diversity in the presentation of the McCune-Albright syndrome, with an unusual bone disease, skin lesions, and a broad panoply of endocrine dysfunction, suggests that there is a basic defect of regulation of cellular function and growth. The nature of the genetic defect remains unknown, but speculation has centered on an altered regulation of intracellular cyclic adenosine monophosphate action.[36] It has recently been shown that patients with bony lesions and pseudohypoparathyroidism (Albright's hereditary osteodystrophy) have reduced stimulatory G protein in many cells, resulting in the diminished generation of hormone-stimulated cyclic adenosine monophosphate.[37]

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Revenge of the Barbecue Grill
Carbon Monoxide Poisoning

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Carbon monoxide (CO) poisoning can be difficult to recognize because it often has a presentation that suggests a viral illness, food poisoning, gastroenteritis, or even a functional illness. Because CO is the leading cause of death due to poisoning in the United States,[1-3] emergency department physicians should suspect CO poisoning when a similar illness occurs simultaneously in two or more persons.

Report of Cases

Four members of a non-English-speaking family presented to a university hospital emergency department, all complaining of headache, lethargy, abdominal cramping, and nausea. They related a history of drinking unrefrigerated milk the evening before presentation. Two patients had mild orthostatic blood pressure changes. They were treated with intravenous fluids and discharged with the diagnosis of infectious gastroenteritis. One family member remained in the emergency department with persistent symptoms.

Several hours later, four other members of the same family presented to the emergency department with similar complaints. They were evaluated and treated with intravenous fluids, and all were discharged, including the patient from group 1. Several hours later, four more members of the same family presented to the emergency department with similar complaints. One patient had not ingested the suspected milk, but she suffered from migraine headache and thought that this was one of her headaches.

Further questioning through an interpreter revealed that all patients were members of the same household. Specific questions about home heating systems did not suggest mechanical problems; in fact, it had not been used. An unaffected relative, who lived elsewhere, admitted to cooking indoors with charcoal briquets in the fireplace after originally stating that the cooking was done outdoors.

Specimens were drawn for arterial blood gas determinations and carboxyhemoglobin (COHb) concentrations. Results were 0.069, 0.151, 0.171 and 0.174 (normal <0.150).* The four patients in the emergency department were treated with 100% oxygen for two hours with symptomatic improvement. The COHb concentration was rechecked in the patient who had a 0.174 level, and it had fallen to 0.044 (4.4%). Fire fighters were dispatched to check the house and reported a barbecue grill in the middle of the living room and evidence of smoke damage.

Discussion

Carbon monoxide is the leading cause of death due to poisoning in the United States.[1-3] It is also the most common cause of death in combustion-related inhalation injury. Claude Bernard in 1857 provided the first accurate description of CO poisoning. Since then many advances in our understanding of the pathophysiology have been achieved.

Carbon monoxide combines preferentially with hemoglobin to produce COHb, displacing oxygen and reducing the systemic arterial oxygen content. Possible mechanisms of toxicity include a decrease in the oxygen-carrying capacity of blood, alteration of the dissociation characteristics of oxyhemoglobin so that delivery to the tissues further decreases, and a decrease in cellular respiration by binding with cytochrome a_3.

Goldbaum and co-workers postulated that high dissolved CO concentrations develop only at the alveolar-blood interface when CO is inhaled. Dissolved CO delivered to tissues, especially heart and brain, causes most of the CO toxicity by binding with the cytochrome a_3.[4] Hence, it is dissolved CO, not COHb, that causes toxic reactions.

The half-life of COHb is 320 minutes for young healthy volunteers breathing room air. Administering 100% oxygen at 1 atm reduces the half-life to 80.3 minutes, whereas 100% oxygen at 3 atm will reduce the half-life to 23.3 minutes.[5]

Carbon monoxide binds to cardiac and skeletal myoglobin and hemoglobin. Cardiac myoglobin binds three times more CO than skeletal myoglobin.[6] Because carboxy-

(Gasman JD, Varon J, Gardner JP: Revenge of the barbecue grill—Carbon monoxide poisoning. West J Med 1990 Dec; 153:656-657)

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*In Système International units, these values are expressed as a fraction of 1. In conventional units, they would be 6.9%, 15.1%, 17.1%, and 17.4%.

myoglobin dissociation is slower than COHb due to its increased affinity for myoglobin, a "rebound effect" with a delayed return of symptoms can occur.[7]

Carbon monoxide poisoning does not cause dyspnea or tachypnea until it causes hypoxemia from circulatory dysfunction or lactic acidosis from tissue hypoxia. At low levels, chronic cardiopulmonary problems, for example, angina and chronic obstructive pulmonary disease, may be exacerbated because cardiac myoglobin binds with great affinity and rapidly reduces myocardial oxygen reserve.

With acute exposure, blood levels correlate with symptoms and signs but do not reflect tissue CO levels. Arterial blood gas levels are used to determine the degree of carbon monoxide intoxication and treatment.[8,9] With levels less than 0.10 (10%), patients are usually asymptomatic. As the COHb concentration increases above 0.20 (20%), headache, dizziness, confusion, and nausea may develop. Chest pain due to myocardial ischemia may occur, as can cardiac arrhythmias. Coma and seizures due to cerebral edema are common with concentrations of greater than 0.40 (40%), and death is likely with more than 0.60 (60%).[10-12]

The differential diagnosis includes viral illnesses, food poisoning, depression, transient ischemic attacks, coronary artery disease, arrhythmias, and functional illnesses, among others. The most common misdiagnosis is a "flu-like" syndrome.[9]

The mainstay of therapy is supplemental oxygen and monitoring for cardiac arrhythmias. The goal of oxygen therapy is to improve the oxygen content of the blood by maximizing the fraction dissolved in plasma (Pao_2).[13] The advantage of hyperbaric oxygen therapy is a more rapid reduction in COHb levels. Disadvantages of this treatment modality include few available treatment centers and the requirement for patient transport. Patients with severe neurologic or cardiovascular symptoms or very high COHb concentrations would benefit from hyperbaric oxygen, but it is these very sick patients for whom transport is most hazardous.

Once treatment begins, oxygen therapy and observation must continue long enough to rule out delayed sequelae as the carboxymyoglobin unloads.

The initial presentation of our patients was consistent with gastroenteritis, for which they were given intravenous hydration and other supportive measures. We initially did not consider inhaled toxins. Once an adequate history, which included indoor cooking, and after arterial blood gas results were obtained, they were placed on 100% oxygen therapy with a complete resolution of the symptoms. They were discharged to a safe environment within three hours of the correct diagnosis.

This case illustrates the importance of always considering CO poisoning when two or more patients are similarly or simultaneously sick. The diagnosis must be excluded by a directed history and physical examination. If suspicion remains, COHb testing should be done and oxygen therapy should be started empirically while results are pending. If CO poisoning is confirmed, the source must be identified and recommendations for correction or avoidance made.

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Primary Tuberculous Thyroid Abscess Mimicking Carcinoma Diagnosed by Fine Needle Aspiration Biopsy

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TUBERCULOSIS AFFECTING the thyroid gland is a rare condition. Exact figures for the incidence of tuberculosis of the thyroid are unavailable. The infection may present first in the thyroid gland or appear secondary to a tuberculous process elsewhere in the body. Barnes and Weatherstone noted that 7% of cases of miliary tuberculosis involve the thyroid gland.[1] The gland can also become involved with focal caseating tuberculosis, which can be blood-borne,[2,3] or by direct extension from the larynx and cervical lymph nodes. The pathologic forms include multiple thyroidal granulomata, goiter with caseation, cold abscess, chronic fibrosing thyroiditis, and, least common, acute abscess.[4] Patients present with a thyroid nodule,[5] abscess,[4] thyroiditis,[6] or findings suggesting carcinoma[7] of the thyroid gland.

A tuberculous abscess of the thyroid gland as the sole manifestation of tuberculosis is even more uncommon. Swelling of the neck is the most consistent sign and dysphagia the most common complaint.[3] The diagnosis of a tubercular abscess is rarely made clinically. In the case reported here, the clinical presentation suggested an undifferentiated thyroid cancer or granulomatous disease of the thyroid. Fine needle aspiration biopsy revealed milky fluid, and subsequent cultures confirmed the diagnosis preoperatively.

Report of a Case

The patient, a 61-year-old, asymptomatic, married white woman, was referred to the University of California, San Francisco, Medical Center because of a right neck mass of 1½ months' duration, clinically suggestive of anaplastic

(Magboo MLC, Clark OH: Primary tuberculous thyroid abscess mimicking carcinoma diagnosed by fine needle aspiration biopsy. West J Med 1990 Dec; 153:657-659)

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
HIV = human immunodeficiency virus

carcinoma of the thyroid. She was on thyroxine replacement therapy following a subtotal thyroidectomy in 1958 for Graves' disease. She had otherwise been in excellent health but was upset because the referring surgeon thought by physical examination that she had an invasive thyroid cancer. On physical examination she was anxious but had a normal blood pressure (130/70 mm of mercury), pulse rate (72 beats per minute and regular), and temperature (37.6°C). She had a large, nontender, hard mass in the right lobe of the thyroid gland that was relatively fixed to the adjacent structures. There was no adjacent lymphadenopathy or overlying erythema.

Laboratory test findings included a thyroxine radioimmunoassay of 75 nmol per liter (5.8 μg per dl [normal, 64 to 132]), free thyroxine index 4.9 (normal, 6.5 to 12), and thyroid-stimulating hormone 0.29 units per liter (normal, 0.4 to 4.8). A complete blood count included a hemoglobin of 139 grams per liter (13.9 grams per dl), hematocrit 0.41 (40.9%), and leukocyte count 7.7×10^9 per liter (7,700 per μl). The sedimentation rate was 9 mm per hour. Liver function test results and serum electrolyte levels were normal. Chest radiography was normal. A urine culture was negative for acid-fast bacilli. Ultrasonography of her neck revealed a 3.0- by 2.8- by 1.6-cm mass in the right lobe of the thyroid gland compressing the internal jugular vein (Figure 1). No thyroid gland was noted on the left side.

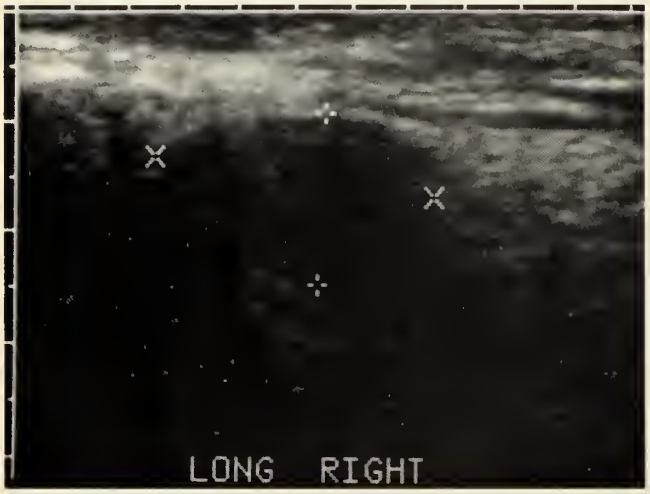

Figure 1.—A 7.5-MHz ultrasonographic scan (longitudinal view) shows a 3.0- by 2.8- by 1.6-cm mass in the right lobe of the thyroid gland. Note the hypoechoic nature of the tuberculous abscess with internal echoes.

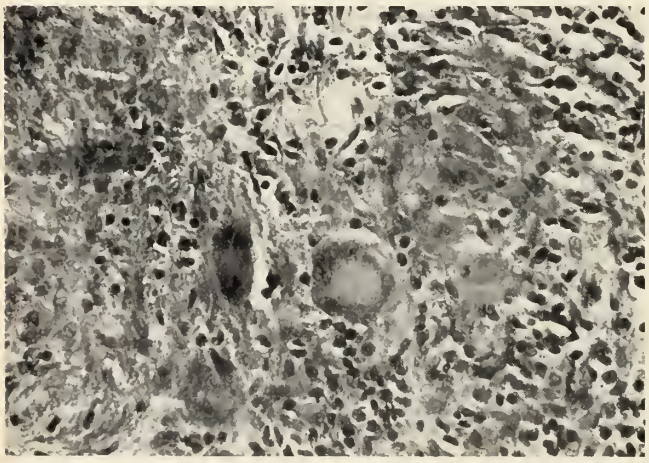

Figure 2.—A photomicrograph of a tissue specimen from the right lobe of the thyroid gland shows acute inflammatory cells, amorphous debris, and multinucleated giant cells (original magnification × 100).

An aspiration biopsy revealed 3 ml of milky white, odorless opalescent material. On cytologic examination there were no tumor cells and the direct smear was negative for bacteria. A month later, culture of the aspirated fluid grew *Mycobacterium tuberculosis.* A month after the aspiration biopsy, the patient had redness and an enlarging, nontender 5- by 3-cm mass in the right thyroid. Fine needle aspiration smears again revealed acid-fast bacilli. The patient was taken to surgery because of the abscess and presumed secondary infection, with erythema and an enlarging thyroid mass, and because of the possibility of an underlying malignant lesion. She underwent incision and drainage of a thyroid abscess with excision of necrotic muscle and part of the right lobe of the thyroid gland. During the operation there was dense brawny induration seen in the subcutaneous tissues extending almost to the skin on the right side of the neck. The muscles and the underlying portion of the thyroid gland were partially destroyed and were necrotic and hemorrhagic. All tissues were matted together so that it was difficult to identify the planes between the sternocleidomastoid muscle and the sternohyoid and sternothyroid muscles. Histologic examination showed granulomatous inflammation with multinucleated giant cells (Figure 2). A direct smear using a Kinyoun stain was positive for polymorphonuclear cells and a few acid-fast bacilli. *M tuberculosis* grew in the culture.

The patient had an unremarkable postoperative course. She was treated with isoniazid, 300 mg per day, and rifampin, 600 mg per day, and has been well without any signs or symptoms of localized or systemic tuberculosis. She has a monogamous relationship and says she does not abuse drugs nor has she had a blood transfusion during the previous ten years.

Discussion

Bruns in 1893 was the first to make the clinical diagnosis of tuberculosis of the thyroid gland in a living patient.[8] The first report of a tuberculous abscess of the thyroid gland was in 1894.[9] There were several reviews of this subject in the literature before 1945.[2,3,10] Our patient's previous thyroid condition and surgical therapy may have been important. Altemeier in 1950 reported that half of the patients with suppurative thyroiditis also had adenomatous goiters, and in these patients the infection was localized rather than diffuse.[11] In 1965 Goldfarb and co-workers reported the 28th case of a tuberculous thyroid abscess and considered it the first case of tuberculous thyroiditis proved by smears and cultures.[12] Since then, single cases of tuberculous abscess of the thyroid gland have been reported in the English-language literature.[4,7,13-16] Confusion with thyroid cancer,[6,7] acute staphylococcal infection,[15] and subacute thyroiditis[16] is common.

The definitive diagnosis of tuberculosis of the thyroid gland is made by demonstrating the presence of tubercle bacilli either by histologic examination, bacterial culture, or animal inoculation. Berger and associates identified 19 cases of thyroiditis due to *M tuberculosis* and one case each due to *Mycobacterium chelonei* and *Mycobacterium intracellulare.*[17] They noted that most of the previously diagnosed

cases were based solely on the findings of lymphocytic infiltration or granulomata that may accompany other conditions like thyroidal sarcoidosis, granulomatous syphilis, parenchymatous giant cell granulomas, Hashimoto's thyroiditis, carcinoma, and simple invagination of thyroid epithelial rests.

Most of the proven cases of tuberculous involvement of the thyroid gland have been diagnosed either postoperatively or at autopsy. Of 1,200 thyroidectomies in 1926, 5 cases of tuberculous involvement were recorded by Coller and Huggins,[18] whereas 1 among 1,225 was reported by Keynes and Camb in 1918.[19] Of 20,758 tissue specimens examined at the Mayo Clinic between 1920 and 1931, only 21 showed tuberculosis of the thyroid gland.[8] In 1952 Levitt and colleagues found 2 cases of tuberculous involvement of the thyroid among 2,114 partial thyroidectomies.[20] Only 2 cases of tuberculosis of the thyroid were found in 74,393 thyroid specimens at an Italian center between 1941 and 1970.[1]

Making the diagnosis of primary tuberculosis of the thyroid is difficult, but this disorder should be considered in any patient who appears to have an invasive or undifferentiated thyroid cancer. The only initial complaint of our patient was the nodular mass in the thyroid, which was the only site clinically affected by tuberculosis. Cytologic examination of aspirate confirmed the diagnosis.

Extrapulmonary tuberculosis is increasing in frequency in patients with human immunodeficiency virus (HIV)-induced immunosuppression. Patients with tuberculosis and the acquired immunodeficiency syndrome (AIDS) have high rates of extrapulmonary disease ranging from 45% to 75%.[21] Patients with HIV infection are therefore more likely to have tuberculosis of the thyroid or at other extrapulmonary sites. Our patient was questioned about extramarital relationships, blood transfusions, or injections but denied any such factors for AIDS. She refused HIV testing.

To our knowledge, this is the first case of primary thyroid tuberculosis presenting as a cold abscess in which the preoperative diagnosis was made by fine needle aspiration biopsy. This procedure made the diagnosis of malignancy unlikely, and tuberculosis was proved by smears and cultures. The use of fine needle aspiration has been popular in Sweden since the early 1950s.[22] It is the most accurate and cost-effective screening technique for thyroid nodules,[23,24] with an accuracy of the cytologic analyses ranging from 50% to 90%.[25] Until recently, however, some physicians in the United States have been reluctant to adopt fine needle aspiration biopsy as the initial diagnostic step in the evaluation of nodular goiter.[24]

Whenever infection is suspected as the cause of a thyroid nodule, fine needle aspiration biopsy is recommended and cytologic examination, as well as smear and culture for bacterial and fungal infection, should be done. This rapid, simple, and safe office procedure may reveal a surprising origin for a thyroid nodule. With the knowledge of tuberculosis in the thyroid gland, operative treatment can be avoided in most patients.

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Editorials

Parathyroid Hormone-Related Peptide

Malignancy-associated hypercalcemia has been recognized since the early 1920s.[1] This syndrome was initially thought to be the result of local bone destruction mediated by malignant cells in direct contact with bone or bone-resorbing cells. In 1941, Fuller Albright described a patient in whom hypercalcemia and hypophosphatemia resolved following irradiation of a solitary bone metastasis from a renal carcinoma; he proposed that the carcinoma was secreting parathyroid hormone (PTH) or a peptide with similar actions. By the mid-1950s, Albright's humoral hypothesis had been placed on a first-descriptive footing by the reporting of several series of cases in which hypercalcemia was eliminated by the removal or debulking of malignant tumors. In other patients hypercalcemia was clearly associated with an extensive tumor burden in bone. Thus, by 1960 or so there was agreement that malignancy-associated hypercalcemia could result from either of two general mechanisms, one local (referred to as local osteolytic hypercalcemia) and one systemic (referred to as humoral hypercalcemia of malignancy). Until recently, there has been agreement about little else in this field. The key points of controversy included the relative frequencies of the local and humoral mechanisms, reliable clinical criteria for invoking one or the other of these two mechanisms, and the identity of the humoral mediator(s) in patients with malignancy-associated hypercalcemia. For example, through the 1970s it was widely held that the local osteolytic syndrome was far more common than the humoral syndrome, that the presence of one or more bone metastases signified local osteolytic hypercalcemia by definition, and that humoral hypercalcemia was predominantly due to "ectopic" hyperparathyroidism. Those who hold to these beliefs today are in need of a refresher course and are referred to the excellent summary of the field provided elsewhere in this issue by Strewler and Nissenson.[1]

In the 1980s remarkable progress was made in this area in a series of studies that evolved rapidly through a number of interrelated phases. The first phase involved clinical studies which suggested that humoral hypercalcemia was common and, more important, provided a marker for this syndrome in the form of an increase in nephrogenous cyclic adenosine 3′:5′-monophosphate (AMP) excretion. Because nephrogenous cyclic AMP was thought to reflect specifically the interaction of PTH with its receptors in the kidney, this effect of the putative tumor-derived peptide was regarded as "PTH-like." The second phase of work followed directly from this interpretation and involved the use of PTH-sensitive adenylate cyclase assays to detect the peptide in tumor extracts and in the medium from cultured malignant cells. Using these methods, it was possible to show that humoral hypercalcemia-associated tumors regularly contained PTH-like bioactivity whereas control tumors or those associated with local osteolytic hypercalcemia were devoid of such activity. The third phase involved isolating the PTH-like peptide, a formidable task because of its low abundance even in humoral hypercalcemia-associated tumors. Several groups were successful in purifying minute quantities of the tumor-derived peptide and in using this precious material to gain partial amino-terminal sequence information. Although partial, this sequence was a thing of beauty to those in the field in that it revealed that one portion of the molecule bore a remarkable similarity to the sequence of PTH itself whereas another portion bore no resemblance whatsoever. The fourth phase of work involved the use of molecular techniques to identify complementary DNAs encoding the tumor-derived peptide, revealing its complete structure, and this was followed shortly by the isolation of the human gene. The peptide was found to be about twice the size of native PTH and to have a sequence similarity to PTH confined to its proximal amino terminus; the remainder of its sequence was unique. This structural information permitted the preparation of synthetic peptides that were found to be biologically active in vitro and in vivo and that have also been used to raise region-specific antisera. Although there has been no formal agreement in this field regarding nomenclature, the term PTH-related peptide (PTHrP) seems reasonable on the basis of what is known.

Based on chromosomal localization findings and shared structural features, the PTH and PTHrP genes seem to have arisen by duplication from a common ancestral precursor and to therefore represent members of a gene family. Following this duplication event, the PTH and PTHrP genes have clearly evolved separately. The PTH gene has a comparatively simple structure and appears to be expressed exclusively by parathyroid cells. The parathyroid hormone has, of course, a well-defined, restricted job description and is associated with well-known syndromes of hormone deficiency and excess. In contrast, the human PTHrP gene has evolved a highly complex structure and appears to be expressed in a remarkable array of normal tissues. The structural complexities of the gene include alternatively spliced exons that give rise to three different PTHrP isoforms. The number of normal tissues that have been found to express the PTHrP gene seems to grow by the week and includes sites as diverse as keratinocytes, the endocrine pancreas, discrete regions of the central nervous system, and a number of reproductive tissues. In reproductive tissues such as lactating breast and preterm myometrium,[2] the expression of the gene is clearly under the control of normal physiologic stimuli—such as a suckling in the case of a lactating breast. Exactly what the PTHrP is doing in all of these sites or circumstances is unknown, but its actions are almost certainly local (autocrine or paracrine) rather than systemic. In a number of sites, the role of the peptide may involve calcium translocation, signaling, or both. Presumably these actions are mediated by unique PTHrP receptors, but such receptors have yet to be identified.

It may well be that the only circumstance in which the PTHrP enters the systemic circulation in sufficient quantities to exert a conventional "endocrine" effect is in the specific pathophysiologic setting of the syndrome of humoral hypercalcemia of malignancy. In this setting the peptide is clearly interacting or cross-reacting with classic PTH receptors in bone and kidney. In a nutshell, these receptor interactions explain the salient clinical and biochemical features of humoral hypercalcemia of malignancy. A number of these features—such as uncoupled bone turnover and reduced circulating levels of 1,25-dihydroxyvitamin D—differ from those in primary hyperparathyroidism and may result either from the severity of the process in humoral hypercalcemia or from the differing structures of circulating PTHrP and PTH. As noted above, it is doubtful that this scenario of PTHrP "cross-talk" with PTH receptors is relevant to the normal physiologic role of the PTHrP, in that

mounting evidence suggests that this role is predominantly local.

Despite the great progress that has been made in this area in the past decade, there is much of importance that remains unknown. We do not know what constitutes the final secretory form of the PTHrP for any cell type. This is a complicated question because different PTHrP isoforms exist and also because these isoforms may be subject to cleavage or other forms of processing. It is not unlikely that individual cell types may process PTHrP in a cell-specific manner and secrete quite different products. We do not know exactly how PTHrP acts, and unique PTHrP receptors have yet to be identified. Progress in this area has been hampered by the lack of information concerning the secretory form of the peptide. We do not understand the precise role(s) of the PTHrP in any of the many tissues in which it is produced, although there are some interesting leads in this regard. A peptide in search of a function is not an easy problem, particularly at a local level, so that this area of investigation may require many more years of study. We do not understand why certain malignant cells of a given cell type express the PTHrP gene whereas others do not. A related question is why the PTHrP gene is so commonly expressed and the PTH gene so rarely expressed by malignant cells. This is an important question of tumor cell biology that clearly cuts through previously simplistic concepts concerning eutopic versus ectopic gene expression.

What effect will progress in this area have on clinical medicine? Immunoassays for PTHrP are already becoming available and should simplify the differential diagnosis. Second-generation assays of greater sensitivity may also prove useful in detecting low circulating concentrations of PTHrP that may serve as a tumor marker in patients who do not have hypercalcemia. Some interesting structure-function work is being done with hybrid PTH-PTHrP sequences, and there is the long-range hope that potent competitive inhibitors will be developed. Finally, if the PTHrP turns out to have widespread local actions, there is the possibility that other forms of disease may someday be explained on the basis of lesions in these local signaling pathways.

In summary, a novel PTH-related peptide has been discovered by virtue of its production by tumors associated with the syndrome of humoral hypercalcemia of malignancy. In certain ways, this problem is reminiscent of the discovery of the growth hormone-releasing hormone (GRH) in human pancreatic tumors several years ago,[3,4] the principal difference being that GRH had a defined role before its actual isolation whereas the normal role of the PTHrP is not yet known. The PTHrP problem has moved extremely rapidly and has been an exciting area in which to work; scarcely ten years passed between the initial identification of a viable marker for the effects of the peptide in vivo and the isolation of the human PTHrP gene. In addition to providing an answer to a rather old question, the solving of this problem stands as an excellent example of the power of the marriage between modern technology and clinical observation.

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Correspondence

The Editors will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words and must be typewritten, double-spaced, and submitted in duplicate (the original typescript and one copy). Authors will be given the opportunity to review the editing of their correspondence before publication.

Total Parenteral Nutrition

To THE EDITOR: We have read with interest the survey by Katz and Oye[1] from our institution. We agree that total parenteral nutrition (TPN) may at times be overused at our and other institutions. The conclusions made by the authors on the patients surveyed are not necessarily valid, however. First of all, the authors failed to evaluate the clinical outcome in the patients they studied. They assumed their heterogeneous sample to reflect that of previous studies, some of which showed a lack of efficacy involving specific patient groups. In essence, a historical control was used, which may not have been applicable to the group surveyed by Katz and Oye. In addition, the authors failed to separate perioperative TPN into preoperative and postoperative. Mullen and colleagues have shown that preoperative TPN of as little as seven days' duration is effective in reducing morbidity and mortality in a heterogeneous group of surgical patients.[2] In addition, Williams and co-workers found significantly fewer wound infections in patients who had received TPN for as little as seven days as compared with controls.[3] Starker and colleagues found a clear reduction in postoperative morbidity in malnourished patients receiving even seven days of nutritional support.[4] They note that the length of time required for preoperative complications varies among patients and must be individualized. We agree. Therefore, a blanket claim by Katz and Oye that all patients who received only seven days of TPN received it inappropriately is misleading and incorrect. Unfortunately, these authors provide no information on the outcomes of the inpatients.

Askanazi and co-workers have evaluated the results of using seven days of postoperative TPN on the length of hospital stay.[5] These authors found a significant decrease (from a mean of 24 days to 17 days) in the time spent in hospital for patients undergoing radical cystectomy who were supported with TPN. Again, no information on hospital duration is provided by Katz and Oye.

In addition, Katz and Oye selected seven days as the minimal need for duration of TPN administration without regard to their patients studied and without consulting more recent literature. Young and colleagues clearly showed that preoperative TPN significantly increased the capacity for hepatic protein synthesis measures by ^{14}C-leucine incorporation in the liver after only three days of support. Plasma amino acid, fibronectin, and immunoglobulin A levels were also noted to increase following three days of TPN administration.[6]

Katz and Oye also incorrectly assume that intravenous TPN is often inappropriate because it supplies fewer calories. In smaller patients, peripheral TPN is often more than adequate to supply caloric and protein requirements. We usually supply patients with up to 1,520 kcal and 100 grams of protein daily with a regimen of peripheral TPN, which, incidentally, is associated with fewer complications than TPN by central catheter. Finally, these authors assume that because patients had oral intake after seven days, this was adequate to meet their needs, yet they list no data on caloric counts or ability to tolerate enteral feeding.

Katz and Oye present interesting data. One cannot conclude, however, that patients who received TPN intravenously or centrally for seven days or less received it inappropriately. More information is needed on the economics of hospital stay duration, complications, and ability to tolerate enteral feeding in this patient group before such a conclusion can be justified. Total parenteral nutrition administered for less than seven days may not be clinically beneficial; however, it is unclear from the present study whether its use is truly inappropriate.

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* * *

Drs Katz and Oye Respond

We agree with Buchman and Ament that the effectiveness of parenteral nutrition should be based on outcome. Our retrospective review of parenteral nutrition use was designed to determine what proportion of use in a university hospital followed the guidelines that have been recommended by the American Society of Parenteral and Enteral Nutrition and the American College of Physicians. We used a conservative criterion of seven days because both organizations cite a range of seven to ten days needed for appropriate support. Our study was not intended to evaluate outcomes, nor would such information be meaningful given the study design.

The literature on preoperative parenteral nutrition cited by Buchman and Ament is selective and not particularly relevant to our patient population. Of 72 surgical patients included in our review, only three received parenteral nutrition before surgical procedures were done, and only one received it for more than two days. This suggests that in the era of prospective payment, preoperative use represents a minute proportion of use of this therapy.

The article by Askanazi and co-workers addressed the efficacy of postoperative parenteral nutrition.[1] This small, randomized trial of 35 patients undergoing total cystectomy was intended to determine changes in physiologic parameters. In retrospect, the authors noted a shorter length of hospital stay in patients receiving treatment but conceded that this was not due to differences in complications or mortality. Many studies have reported that giving parenteral nutrition changes physiologic parameters. Unfortunately, these observations have not translated easily into substantial improvement in outcomes. Until more definitive studies are completed, such as the Veterans Administration cooperative study on perioperative parenteral nutrition,[2] we should adopt a prudent approach to this therapy.

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Disability and the SSA

To THE EDITOR: It is not uncommon for a treating physician to think that a patient who has been denied Social Security disability benefits truly is disabled. This difference of opinion might be avoided if the treating physician understands how Social Security disability is determined and also understands the importance of documenting the limitations of function imposed by the medical impairment.

Physicians are accustomed to gathering the historical information and results of examination and corroborative laboratory evidence to establish a working diagnosis and treatment program. They are not accustomed to documenting in the medical record the limitation of function that impairment imposes, however.

According to the Social Security Administration (SSA), disability exists when a documented physical or mental impairment would prevent the claimant from performing all types of work for at least 12 months or when the disability could be expected to result in death. The treating physician routinely is requested to furnish medical records or reports to the state agency responsible for processing Social Security disability claims. A quick and thorough response results in the best decision. Once the medical evidence is received, a medical consultant evaluates it and determines whether the claimant's impairment meets or equals "The Listing of Impairments," a booklet containing over 100 medical conditions that the SSA considers disabling. Statutory blindness, brain cancer, and mental retardation with an IQ below 60 are examples. In such cases, both the treating physician and SSA would agree a claimant is disabled.

When an impairment of listing-level severity is not documented, the medical consultant then evaluates what the claimant can do despite the limitations imposed by his or her impairments. This assessment is referred to as the residual functional capacity (RFC) and is expressed in terms of amounts of standing, walking, sitting, lifting, and other work-related abilities the claimant retains. At this point, a disability analyst determines whether the RFC would permit past work. If not, the claimant's age, education, and work experiences are evaluated in relation to the RFC to determine if the claimant can do other kinds of work. Many treating physicians are unaware that two claimants with identical medical conditions could receive opposite disability decisions because of differences in age, education, and vocational background.

The most accurate determination of disability occurs when the treating physician not only provides complete and detailed objective medical evidence regarding a medical condition but also describes the restrictions in function imposed by the impairment, such as in lifting, bending, reaching, walking, standing, sitting, manipulating, hearing, seeing, thinking, and remembering. This medical assessment by the treating physician of the limitations of function is used by the medical consultant for assessing the RFC.

Sometimes the medical consultant or disability analyst telephones the treating physician to discuss the patient's limitations of function, response to treatment, and prognosis, especially when there is pain or weakness due to a medically determined condition documented by objective evidence and it is necessary to determine the extent to which these symptoms limit function. For example, weakness in a person testing positive for the human immunodeficiency virus and having a marked reduction in T4 helper cells, fever, and other symptoms or pain in a person with lumbar disc disease documented by magnetic resonance imaging could limit function.

A treating physician who wishes to aid a patient in a disability claim should be aware of the need to furnish a detailed description that the impairment imposes on function, along with thorough objective evidence that supports the opinion. When this is done, both the patient and society will benefit from the correct decision being made.

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Continuing Stress and Hypertension

To THE EDITOR: Dr Mustacchi has accomplished, in the August issue, a most comprehensive literature review on the subject "Stress and Hypertension."[1] His conclusions, however, were startling and did not match the material gathered in his excellent review. His statement, "It is still unclear if repetitive or continuing stress will induce fixed hypertension," certainly is not justified after a review of the medical literature. His speculation that these "repetitive exposures to stress can result in habituation" is contrary to the literature that he himself reviewed and contrary to clinical impressions that I believe every physician has experienced. I do not believe that a person can get used to a continuum of stress. Indeed, the psychophysiologic responses to stress continue and, if anything, stressed persons react more adversely to stress. Dr Mustacchi's own literature review has shown substantial epidemiologic evidence of hypertension and complications of hypertension, such as strokes in an occupational setting that characteristically has a high stress level. A recent article in *JAMA* showed that persons working with "high job strain" had a substantial increase in the left ventricular mass index as measured echocardio-

graphically. I think there is little doubt that continued, unusual, prolonged emotional stress causes, aggravates, and accelerates hypertension and will lead to left ventricular hypertrophy and complications of hypertension, which will lead to strokes. I think that unremitting stress must be accepted as a risk factor in hypertension and its complications. Dr Mustacchi states, "Plausible hypotheses linking stress to hypertension have been advanced, but the longitudinal information required for a satisfactory validation is not yet available." When does he expect that information will be available? I hold that the evidence is overwhelming. I hold that some persons, however learned as the author, will never be convinced.

It is extremely important that *The Western Journal of Medicine* acknowledge that Dr Mustacchi's reluctance to accept this information as being definite is not shared by any other physicians who regularly encounter this problem.

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* * *

Dr Mustacchi Responds

To THE EDITOR: I wish to thank Dr Markovitz for his appreciative words about my recent review on "Stress and Hypertension."[1] There seem to be, however, two areas in which his beliefs differ from the conclusions of my review. Both deal with occupational stress.

He considers speculative and unjustified the inference that "repetitive exposures to stress can result in habituation."[1] Habituation is a conclusion well supported by the reviewed studies of naval aviators,[2] bus drivers,[3] surgeons and operating room personnel,[4] white and blue collar workers,[5] and air traffic controllers.[6,7]

I consider the epidemiologic evidence I supplied to be both sound and persuasive, although Dr Markovitz seemingly does not find it so. Because he did not reference the studies that prompt his beliefs, I am unable to explain or reconcile these differences.

He also disagrees with my conclusion that "plausible hypotheses linking stress to hypertension have been advanced, but the longitudinal information required for a satisfactory validation is not yet available." He claims that such evidence is "overwhelming" but does not provide the reader with any reference substantiating that assertion. I should point out that when I started searching the literature, I shared his opinion, and I expected to find ample documentation in support of this clinical belief. Not only did my search prove sterile, but, when critically analyzed from the epidemiologic viewpoint of causality, several studies indicated that, if anything, the evidence was on the other side.[3,6,8]

If I have inadvertently overlooked pertinent longitudinal studies known to my colleague, I would be grateful if he would share them with me. He quotes the *JAMA* article, "The Relationship Between 'Job Strain,' Workplace, Diastolic Blood Pressure, and Left Ventricular Mass Index," also quoted by me. This is a cross-sectional study, not a longitudinal one, and when causality is at issue, longitudinal studies are essential. Additional legitimate questions arise about the uncertain significance of a relationship between left ventricular mass and job stress found only in workers aged 30 to 40 but not in those aged 41 to 60.

Some cross-sectional studies render very attractive the conjecture that the transient blood pressure elevations caused by stress lead to sustained hypertension but, as already intimated by Dustan,[10] this hypothesis is still not epidemiologically validated.

Some serious misperception seems to have crept into the last paragraph of the letter when it alludes to my "reluctance to accept this information as being definite." I do not know how this inference was reached. All I can say is that my review brings together the indefinite nature of stress and the definite information contained in the more than 100 reviewed articles. Concern with definitions structures much of epidemiologic thinking, and it is exactly because I considered definite the published information that I sought to define its limits both in extent and character as well as within the framework of the criteria of causality.

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The Peril of Espresso Machines

To THE EDITOR: We read with great interest the letter from Dr Shusterman in the June issue regarding "espresso maker's wrist."[1] We describe another complication of using this machine. A 34-year-old, otherwise healthy man operates a coffee house adjacent to our medical center. One morning while savoring a cappuccino, we noted that he was massaging his right hypothenar eminence with his left hand. Upon inquiry, he complained of dysesthetic pain on the medial aspects of both palms and paresthesias in the ulnar-innervated digits bilaterally, particularly after operating the hand crank of the espresso maker. He was making approximately 100 espresso drinks a day, with each drink requiring four or five movements of the crank arm. On examination, he had normal motor bulk and strength of the upper extremities, with sensory examination revealing diminished light touch and pinprick in the fourth and fifth digits bilaterally. In addition, a positive percussion test over the ulnar nerves at both elbows was noted. Electrical studies showed substantial reduction of motor conduction velocity across

the elbow segments of the ulnar nerves, with the right side slightly more affected.

We observed that cranking the espresso machine's arm involved repeated elbow flexion to 90 degrees against the resistance of the crank arm. This arm position has been previously reported to compromise the ulnar nerve at the elbow due to narrowing of the cubital tunnel.[2] We advised the espresso maker to consider an automated machine, which he purchased. His symptoms of "espresso elbow" gradually resolved, and repeat nerve conduction study results were normal. We are in agreement with Dr Shusterman's conclusion that the appropriate application of alternative work practices can keep workers healthy and, in this case, physicians alert and oriented for morning rounds.

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Clarification

To THE EDITOR: In reading our paper "Pleuropulmonary Manifestations of Hepatic Amebiasis" in the September issue,[1] I noted some editing changes that inadvertently changed the meaning of some of the sentences.

The first sentence of the abstract was edited to read, "Pleuropulmonary manifestations of hepatic amebiasis occurred in 30 patients . . ."; this is misleading. The 30 patients with hepatic amebiasis did not *all* have pleuropulmonary manifestations.

In the tables, the phrase "of 30 Patients With Pleuropulmonary Manifestations of Hepatic Amebiasis" was added to each title and this likewise implies that all 30 patients with hepatic amebiasis had pleuropulmonary manifestations.

The text of the manuscript, as well as the information in the tables, accurately shows the percentages of the patients with hepatic amebiasis who had pleuropulmonary manifestations.

I am sorry that I did not appreciate the effect these editorial changes would have on the text when I reviewed the galley proofs. I apologize for any confusion this may have caused.

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More on Mohs'

To THE EDITOR: I wish to respond to Dr Safrin's letter,[1] responding to a review of Mohs' surgery by Dr Darmstadt and myself.[2] Dr Safrin states that Mohs' surgery is rarely indicated, inefficient, and costly, that the technique does not allow proper assessment of surgical margins, and that Mohs' surgeons are not qualified to interpret Mohs' surgery frozen sections. These assertions are refuted by a large body of medical literature and by pathologists and dermatopathologists with extensive experience with Mohs' surgery.[3] The procedure has attained such wide acceptance that nearly every medical school in the country has a Mohs' surgeon on staff.

Mohs' surgery is frequently the treatment of choice for recurrent, incompletely excised, infiltrating, and ill-defined basal and squamous cell carcinomas.[4-6] It is recommended for treating skin cancers in locations prone to recurrence and in cosmetically important anatomic areas where tissue sparing is essential.[7,8] It is also very effective for treating many other common cutaneous cancers.[2,7] The medical literature solidly demonstrates that Mohs' surgery has the highest cure rate of any therapeutic modality for the treatment of basal cell and squamous cell carcinomas.[4-6] Several large studies of five-year determinant cases report cure rates for basal cell carcinoma using the Mohs' technique exceeding 98%.[5,6]

A major advantage of Mohs' surgery is its efficiency and cost effectiveness. In experienced hands, tissue processing routinely takes only minutes to complete,[9] and this work is done by a specially trained technician. During this time, the patient is in a waiting room, not occupying an operating room. The Mohs' surgeon's time is required only for the surgical procedure and for interpreting the frozen sections. Some pathologists may view the technique as inefficient, time-consuming, or expensive because they do not delegate the processing of the tissue to a trained technician. Compared to the cost of conventional frozen section procedures requiring a surgeon, an operating room and its nursing staff, and a pathologist, Mohs' surgery is not labor-intensive or expensive. Also, when less effective treatments are used, recurrences are more common. These must then be retreated, resulting in further patient morbidity and increased medical costs.

Dr Safrin states that it is impossible to obtain a truly flat, complete Mohs' frozen section, cut parallel to the cryostat's cutting surface, and one must therefore cut excessively into the tissue block. He also suggests that the technique distorts the relationship between adnexal structures and the epidermis and the relationship of tumor foci to the surgical margin. The techniques for preparing Mohs' frozen sections are not routinely known to many pathologists or even licensed histologic technicians. Flat, properly oriented frozen sections from the outermost 100 microns of the surgical margin are the norm in Mohs' surgery and are easily obtained with the proper training and equipment. Moreover, serial sections cut into the tissue block at regular intervals allow for assessment of the relationship of tumor islands and adnexal structures to the surgical margin and the epidermis.

Finally, Dr Safrin questions the competence of Mohs' surgeons to interpret frozen sections accurately. Mohs' surgeons are trained during a one-year postresidency fellowship, where they read thousands of frozen sections from hundreds of Mohs' cases. There are currently 34 such programs accredited by the American College of Mohs' Micrographic Surgery and Cutaneous Oncology. Since nearly all are dermatologists, they also receive three years of formal dermatopathology training during their residency. A recent comprehensive study has shown that Mohs' surgeons are as accurate as general pathologists in interpreting Mohs' frozen sections.[10] Because of the number of frozen sections they review, Mohs' surgeons have far greater experience interpreting horizontally oriented frozen sections of skin

and soft tissue than do most general pathologists or dermatopathologists.

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Lessons From the Practice

Managed Care

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Estevan (Steve) died in August.

He was a cheerful, humorous man with a sparkle in his eye; he always made my day better when he came to the office. I felt he survived his problems by his remarkable outlook on life. As a young man working in a sawmill, he lost an arm and two fingers of his other hand to the tools of his trade; later in life, he developed diabetes and finally struggled with severe congestive cardiomyopathy. Not once do I remember him complaining about his problems.

Steve was a fifth generation member of an Old Town family and proud of his heritage. He and his wife would customarily sit under the cottonwood tree in their yard, smiling and waving to the tourists visiting Old Town. A few years ago, in his late 70s, he broke his leg but insisted on crossing six lanes of traffic on Rio Grande Boulevard with his cast and his walker—to visit his friend at the gas station. Neither his family nor I could dissuade him from going out into that busy street alone, but his family prevailed upon him to wear a fluorescent orange vest on his journey.

Once, on a trip to Old Town, my family and I stopped by to visit. Wearing a buckskin jacket and beaded hatband, I wondered whether my attire was appropriate, even for a spur of the moment visit. "Hey, Geronimoooo!" he greeted me as I entered the kitchen and our families exchanged pleasantries. My fashion concerns alleviated, we had a delightful conversation, as usual. Steve's eyesight was poor and his partial deafness was worse than usual that day. It was only later I learned that he had not recognized me as his physician. He thought I was his friend from the gas station. I thought how wonderful that Steve treated everyone, not just me, to his cheerful, vibrant personality. It also felt good to be included in his world as someone other than his physician.

Steve was admitted to hospital with pulmonary edema, and none of the standard therapies were working. Gasping for air, he said, "Call David." Following his wishes, I summoned his stepson, a physically powerful, gentle, religious man, and told him of the insurmountable problems. David sat at Steve's bedside holding his hand and comforting him with words and gestures. He notified countless other family members so they, too, could be with Steve in his final hours. I took Steve's nurse aside—a young man probably just recently graduated—and told him there was little we could do to save this man's life but much we could do to offer support and comfort to Steve and his family. Though young and accustomed to operating the most sophisticated instruments medical technology has to offer, the nurse focused his efforts on making Steve comfortable and serving the family's needs. Such caring and compassion for a stranger made me realize why nurses are so special and why simple attention to the physical and emotional needs of patients and their families is so crucial to the art of nursing.

As a general internist in a high-technology, specialty-oriented hospital, I sometimes feel like a square peg trying to fit into a round hole—the nursing staff in the critical care areas often suggest all sorts of wonderful, high-tech, aggressive procedures, monitoring devices, or specialists to help me "manage" my patients. But Steve had made it plain to his family and me that he wanted no machines at the end of his life.

About 1 AM, we called for Father Klein to administer the Sacraments. I was impressed by his kindness and his charitable demeanor, even at that hour. Though I was raised a Lutheran, I felt like confessing to Father Klein that I have not always responded with such grace in the middle of the night and asking for help in doing better. When told that Steve hadn't recently been going to church regularly, Father Klein reassured Steve and his family that God was undoubtedly present with him under that cottonwood tree in his yard and not to worry. Steve improved some during the night but died the next morning, surrounded by his family and his nurse, who stayed beyond his shift.

Steve had mastered the art of living and, I believe, knew something of *ars moriente* as well. His enjoyment of life despite his handicaps and illnesses verifies the power of one's outlook on life. His joy in life rubbed off on all of us who knew him and made us better. I believe the final scene of his life—dying with a loving family at his bedside, with an admiring nurse, clergyman, and physician present—was made possible only by the artistry of his life. He brought out the best in people throughout his life and did the same in his dying hours. I was fortunate indeed to have been his physician.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
STEPHEN J. McPHEE, MD
Series' Editors

(Silbaugh BR: Managed care. West J Med 1990 Dec; 153:667)

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The editors wish to acknowledge with appreciation the valued services, beyond those of members of the Editorial Board, given by the following persons to the journal during the past year.

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8. O'Connell M: A Controlled Trial of Regional Intra-arterial FUDR Versus Systemic 5FU for the Treatment of Metastatic Colorectal Cancer Confined to the Liver. Presented at the annual meeting of the American Society of Clinical Oncology, San Francisco, December 1989

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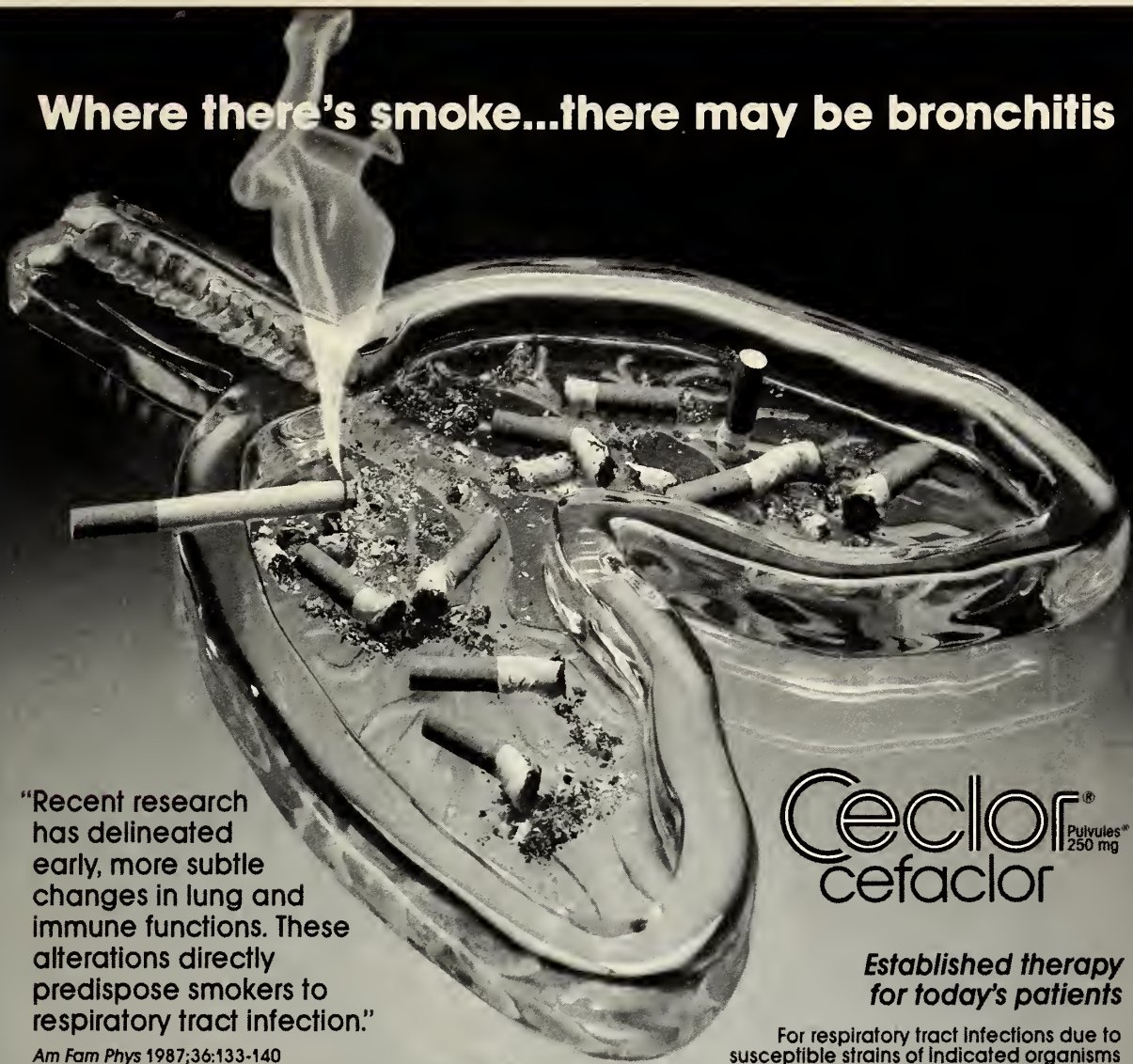

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Indication: Lower respiratory infections, including pneumonia, caused by *Streptococcus pneumoniae, Haemophilus influenzae,* and *Streptococcus pyogenes* (group A β-hemolytic streptococci).
Contraindication: Known allergy to cephalosporins.
Warnings: CECLOR SHOULD BE ADMINISTERED CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. PENICILLINS AND CEPHALOSPORINS SHOW PARTIAL CROSS-ALLERGENICITY. POSSIBLE REACTIONS INCLUDE ANAPHYLAXIS.

Administer cautiously to allergic patients.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics. It must be considered in differential diagnosis of antibiotic-associated diarrhea. Colon flora is altered by broad-spectrum antibiotic treatment, possibly resulting in antibiotic-associated colitis.

Precautions:
• Discontinue Ceclor in the event of allergic reactions to it.
• Prolonged use may result in overgrowth of nonsusceptible organisms.
• Positive direct Coombs' tests have been reported during treatment with cephalosporins.
• Ceclor should be administered with caution in the presence of markedly impaired renal function. Although dosage adjustments in moderate to severe renal impairment are usually not required, careful clinical observation and laboratory studies should be made.
• Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.
• Safety and effectiveness have not been determined in pregnancy, lactation, and infants less than one month old. Ceclor penetrates mother's milk. Exercise caution in prescribing for these patients.

Adverse Reactions: (percentage of patients)

Therapy-related adverse reactions are uncommon. Those reported include:
• Hypersensitivity reactions have been reported in about 1.5% of patients and include morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs' tests each occur in less than 1 in 200 patients. Cases of **serum-sickness-like** reactions have been reported with the use of Ceclor. These are characterized by findings of erythema multiforme, rashes, and other skin manifestations accompanied by arthritis/arthralgia, with or without fever, and differ from classic serum sickness in that there is infrequently associated lymphadenopathy and proteinuria, no circulating immune complexes, and no evidence to date of sequelae of the reaction. While further investigation is ongoing, **serum-sickness-like** reactions appear to be due to hypersensitivity and more often occur during or following a second (or subsequent) course of therapy with Ceclor. Such reactions have been reported more frequently in children than in adults with an overall occurrence ranging from 1 in 200 (0.5%) in one focused trial to 2 in 8,346 (0.024%) in overall clinical trials (with an incidence in children in clinical trials of 0.055%) to 1 in 38,000 (0.003%) in spontaneous event reports. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy; occasionally these reactions have resulted in hospitalization, usually of short duration (median hospitalization = two to three days, based on postmarketing surveillance studies). In those requiring hospitalization, the symptoms have ranged from mild to severe at the time of admission with more of the severe reactions occurring in children. Antihistamines and glucocorticoids appear to enhance resolution of the signs and symptoms. No serious sequelae have been reported.
• Stevens-Johnson syndrome, toxic epidermal necrolysis, and anaphylaxis have been reported rarely. Anaphylaxis may be more common in patients with a history of penicillin allergy.
• Gastrointestinal (mostly diarrhea): 2.5%
• Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment.
• As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.
• Rarely, reversible hyperactivity, nervousness, insomnia, confusion, hypertonia, dizziness, and somnolence have been reported.
• Other: eosinophilia, 2%; genital pruritus or vaginitis, less than 1% and, rarely, thrombocytopenia and reversible interstitial nephritis.

Abnormalities in laboratory results of uncertain etiology.
• Slight elevations in hepatic enzymes.
• Transient lymphocytosis, leukopenia, and, rarely, hemolytic anemia and reversible neutropenia.
• Rare reports of increased prothrombin time with or without clinical bleeding in patients receiving Ceclor and Coumadin concomitantly.
• Abnormal urinalysis; elevations in BUN or serum creatinine.
• Positive direct Coombs' test.
• False-positive tests for urinary glucose with Benedict's or Fehling's solution and Clinitest® tablets but not with Tes-Tape® (glucose enzymatic test strip, Lilly).

PA 8791 AMP [021490LRI]

Additional information available to the profession on request from Eli Lilly and Company, Indianapolis, Indiana 46285.

Lilly

Eli Lilly Industries, Inc
Carolina, Puerto Rico 00630
A Subsidiary of Eli Lilly and Company
Indianapolis, Indiana 46285

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Shown left to right are Jeffrey Cooper, M.D.; Michael Norris, M.D.; William Naftel, M.D.; Darrell Cannon, M.D.; John Ingram, M.D.

LIKE THE COAST UROLOGICAL GROUP.

Members of the Coast Urological Group are among the 3,500 physicians and surgeons who belong to CAP/MPT—The Cooperative of American Physicians, Inc./Mutual Protection Trust.

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Depending on specialty, our members save up to 60% on the cost of their professional liability protection.

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WE WORK HARD AT KEEPING CLAIMS DOWN TO STOP COSTS FROM GOING UP.

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That is one reason why we have had more members and fewer suits filed per 100 members each year since 1985.

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We provide our members with highly qualified defense counsel who must follow stringent written performance guidelines.

For members' convenience, we have four CAP/MPT offices throughout California.

How well does all this work? Because of their good claims experience, over 40% of our members save an additional 10% off our already low rates.

To learn how much you can benefit with CAP/MPT, call us toll-free at (800) 252-7706 in southern California. In northern California, call (800) 848-3366.

And see why the Coast Urological Group and over 3,500 other California physicians put their trust in us.

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MUTUAL PROTECTION TRUST

Cooperative of American Physicians, Inc.
Mutual Protection Trust
Headquarters: Los Angeles
Offices: Orange, San Diego, Burlingame

*The Mutual Protection Trust (MPT) is an unincorporated interindemnity arrangement among physicians authorized by Section 1280.7 of the California Insurance Code. Members do not pay insurance premiums. Instead, they pay tax-deductible assessments based on risk classification and number of months of coverage for the amounts necessary to pay claims and administrative costs. Members also make a tax-deductible initial trust deposit, which is refundable according to the terms of the trust agreement.

(Continued from Page 617)

April 5-6—**Annual Ambulatory Pediatrics.** UCD at Radisson Hotel, Sacramento. Fri-Sat. Contact: UCD.

April 18-19—**10th Annual Child Abuse.** UCD at Radisson Hotel, Sacramento. Thurs-Fri. Contact: UCD.

May 16-18—**24th Annual Advances and Controversies in Clinical Pediatrics.** UCSF at Fairmont Hotel, San Francisco. Thurs-Sat. Contact: UCSF.

PSYCHIATRY

January 27-February 1—**17th Annual Midwinter Program for Psychiatrists: Special Focus on Psychic Trauma.** UCD at Hyatt Regency, Incline Village, Nevada. Sun-Fri. 25 hrs. $395. Contact: UCD.

February 23-24—**The Male Mystique: New Perspectives on the Psychology of Men.** San Diego Psychoanalytic Society and Institute at Hotel del Coronado, San Diego. Sat-Sun. Contact: Joyce Harding, SDPSI, 1010 Turquoise St, Ste 320, San Diego 92109-1259. (619) 488-0687.

February 28-March 1—**The Dimensions of Caring 1991: A Symposium on Palliative Care of the Cancer Patient.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Fri. Contact: Laurie Jones, Box 400S, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-9592.

April 27-28—**The Cutting Edge: Being a Better Therapist.** UCSD at La Jolla Marriott, San Diego. Sat-Sun. Contact: Cass Jones, 7916 Convoy Ct, San Diego 92111. (619) 565-9921.

RADIOLOGY

January 13-18—**Neuro and Musculoskeletal MR Applications.** UCSF at Hyatt Regency, Kauai, Hawaii. Sun-Fri. 24 hrs. $595. Contact: UCSF.

January 19-21—**Advanced Seminars in Diagnostic Imaging.** UCSF at Ritz-Carlton Resort Hotel, Laguna Niguel. Sat-Mon. 20 hrs. $400. Contact: UCSF.

February 1-3—**43rd Midwinter Radiological Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Fri-Sun. 17 hrs. $395. Contact: LARS, PO Box 91215, Los Angeles 90009-1215. (213) 827-9078.

February 4-5—**Angio-Interventional Radiology.** UCSD at Le Meridien Hotel, San Diego. Mon-Tues. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

Feburary 4-8—**Magnetic Resonance Imaging in the Desert.** UCSF at Ritz-Carlton, Rancho Mirage. Mon-Fri. 22 hrs. $595. Contact: UCSF.

February 5-9—**17th Annual Mid-Pacific Radiological Conference.** Los Angeles Radiological Society at Maui Marriott Hotel, Maui, Hawaii. Tues-Sat. 16 hrs. $395. Contact: LARS, PO Box 91215, Los Angeles 90009. (213) 827-9078.

February 6—**Intraluminal Ultrasound.** UCSD at Le Meridien Hotel, San Diego. Wed. 6 hrs. $150. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 6-9—**Introduction to Doppler Principles.** UCSD at Le Meridien Hotel, San Diego. Wed-Sat. 7 hrs. $150. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 6-9—**Duplex Imaging.** UCSD at Le Meridien Hotel, San Diego. Wed-Sat. 22 hrs. $495. Contact: UCSD.

February 9-10—**Obstetric and Gynecology Sonographic Update: Focus on CNS Abnormalities.** UCSD at Le Meridien Hotel, San Diego. Sat-Sun. 10 hrs. $150. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 11-15—**Contemporary Diagnostic Imaging Featuring MRI, CT, US and Interventional Radiology.** Stanford University at Ritz-Carlton Hotel, Mauna Lani, Hawaii. Mon-Fri. 20 hrs. $515. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 1-3—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton Resort Hotel, Laguna Niguel. Fri-Sun. 18 hrs. $400. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 4-8—**Magnetic Resonance Imaging.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 27 hrs. $500. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 16-18—**Breast Imaging Update.** UCSF at Fairmont Hotel, San Francisco. Sat-Mon. 16 hrs. $350. Contact: UCSF.

April 7-12—**Diagnostic Imaging: 1991.** UCSF at Ritz-Carlton Mauna Lani, Kona, Hawaii. Sun-Fri. 23 hrs. $595. Contact: UCSF.

April 21-26—**11th Annual San Diego Resident's Radiology Review Course.** UCSD at Hyatt Regency Hotel, La Jolla. Sun-Fri. 39 hrs. $435. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

April 27—**Introduction to Interventional Radiology.** UCSD at Hyatt Regency Hotel, La Jolla. Sat. 8 hrs. $100. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

REHABILITATIVE/THERAPEUTIC

January 23-26—**6th International Symposium on Platinum and Other Metal Coordination Compounds in Cancer Chemotherapy.** UCSD at Sheraton Harbor Island East Hotel, San Diego. Wed-Sat. Contact: Cass Jones, 7916 Convoy Ct, San Diego 92111. (619) 565-9921.

February 7-9—**Biotherapy of Cancer: A Symposium for Clinicians and Nurses.** Hoag Hospital at Newport Beach Marriott. Thurs-Sat. 15 hrs. $375. Contact: Nomi Feldman, 5665 Oberlin Dr, Ste 110, San Diego 92121. (619) 453-6222.

February 18-20—**11th Betty Ford Center Conference on Chemical Dependency.** Annenberg Center for Health Science. Mon-Wed. Contact: ACHSE, 39000 Bob Hope Dr, Rancho Mirage 92270. (800) 321-3690.

March 6-8—**11th Annual Current Approaches to Radiation, Oncology, Biology and Physics.** UCSF at Hotel Nikko, San Francisco. Wed-Fri. 18 hrs. $325. Contact: UCSF.

May 17-18—**What's New in Rehabilitation?** Memorial/UCI Center for Health Education at Queen Mary, Long Beach. Fri-Sat. Contact: UCI.

SURGERY

December 1990-May 1991—**Temporal Bone Surgical Dissection Courses.** House Ear Institute. 5 days per month. 53 hrs. $975. Contact: Antonio de la Cruz, MD, 2100 W Third St, Los Angeles 90057. (213) 483-4431, ext. 7079.

January 18-19-**What's New in General Surgery: 13th Annual Postgraduate Course.** UCD at Capitol Plaza Holiday Inn, Sacramento. Fri-Sat. 14 hrs. $260. Contact: UCD.

May 2-4—**Advances in Knee Reconstruction Surgery: Ligament Reconstruction, Unicompartmental Replacement, and Patellofemoral Joint.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Sat. 26-hrs. $600. Contact: Susan Buntjer, 400S, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

May 15-19—**13th Annual Wound Management Workshop: May.** UCSD at San Diego Hilton Beach and Tennis Resort. Wed-Sun. 19 hrs. Contact: UCSD.

MULTIPLE TOPICS

March 7-9—**Recent Advances in Geriatric Medicine: New Treatment Options for Old Problems.** UCSD at Pan Pacific Hotel, San Diego. Thurs-Sat. Contact: Cass Jones, 7916 Convoy Ct, San Diego 92111. (619) 565-9921.

March 22-23—**Gender Differences in Nutrition: Annual Clinical Nutrition Program.** UCD at Embassy Suites, Napa. Fri-Sat. Thurs-Fri. Contact: UCD.

April 25-28—**Nevada State Medical Association Annual Meeting.** NSMA at Quail Lodge, Carmel. Thurs-Sun. Contact: Nevada State Medical Association, 3660 Baker Ln, Reno, NV 89502. (702) 825-6788.

February 20-23—**The Practicing Physician's Approach to the Difficult Headache Patient.** Scripps Clinic and Diamond Headache Clinic at Wyndham Hotel, Palm Springs. Wed-Sat. 15 hrs. Contact: Idell Applebaum, 5252 N Western Ave, Chicago, IL 60625. (312) 878-5558.

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COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

January—**Perinatal Continuing Education Program.** The Children's Hospital, Denver Community Hospital-based, 40-week, self-study program for all perinatal healthcare providers. Contact: Pat Winter, (303) 861-6668.

January 17—**Colorado Radiological Society.** Hyatt Regency DTC, Denver. Thurs. Contact: Carol Goddard, (303) 770-6048.

January 26-31—**Uvetitis and Pathology.** Colorado Ophthalmological Society at Westin Hotel, Vail. Sat-Thurs. Contact: Carol Goddard, (303) 770-6048.

February 6-10—**Update on Clinical Allergy: Immunology.** National Jewish Center for Immunology and Respiratory Medicine at Keystone Resort, Keystone. Wed-Sun. Contact: Jeri Wagner, (303) 398-1828.

February 9-16—**16th Annual Psychiatry Conference.** Rose Medical Center at Lion Square Lodge, Vail. One week. Contact: David R. Scott, Rose Medical Center Conference Program, 1 (800) 525-5810.

February 9-16—**13th Annual Emergency Medicine Conference.** Rose Medical Center at Marriott's Mark Resort, Vail. One week. Contact: David R. Scott, 1 (800) 525-5810.

February 16-23—**17th Annual Obstetrics and Gynecology Conference.** Rose Medical Center, Marriott's Mark Resort, Vail. One week. Contact: David R. Scott, 1 (800) 525-5810.

February 16-23—**16th Annual Internal Medicine Conference.** Rose Medical Center at Lion Square Lodge, Vail. One week. Contact: David R. Scott, 1 (800) 525-5810.

February 23-March 2—**16th Annual General Surgery Conference.** Rose Medical Center at Marriott's Mark Resort, Vail. One week. Contact: David R. Scott, 1 (800) 525-5810.

February 23-March 2—**Fourth Annual Medical Care in the '90s Conference.** Rose Medical Center at The Antlers at Vail, Vail. One week. Contact: David R. Scott, 1 (800) 525-5810.

March 2-9—**13th Annual Pediatrics Conference.** Rose Medical Center at Marriott's Mark Resort, Vail. One week. Contact: David R. Scott, 1 (800) 525-5810.

March 2-9—**Second Annual Infectious Disease Conference.** Rose Medical Center at The Antlers at Vail, Vail. One week. Contact: David R. Scott, 1 (800) 525-5810.

March 9-16—**16th Annual Primary Care Conference.** Rose Medical Center at Marriott's Mark Resort, Vail. One week. Contact: David R. Scott, 1 (800) 525-5810.

March 9-16—**Second Annual "Minding the Body, Mending the Mind: Influencing Health and Healing" Conference.** Rose Medical Center at The Antlers at Vail, Vail. One week. Contact: David R. Scott, 1 (800) 525-5810.

March 16-23—**14th Annual Urology Conference.** Rose Medical Center at Marriott's Mark Resort, Vail. One week. Contact: David R. Scott, 1 (800) 525-5810.

March 16-23—**13th Annual Sports Medicine Conference.** Rose Medical Center, Marriott's Mark Resort, Vail. One week. Contact: David R. Scott, 1 (800) 525-5810.

March 16-23—**Computers in Medicine Conference.** Rose Medical Center at The Antlers at Vail, Vail. One week. Contact: David R. Scott, 1 (800) 525-5810.

March 23-30—**14th Annual Cancer Treatment Conference.** Rose Medical Center at The Antlers at Vail, Vail. One week. Contact: David R. Scott, 1 (800) 525-5810.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver, CO. (303) 270-5195.

IDAHO

February 27-March 2—**Sun Valley Program.** Pierce County Medical Society (Washington) College of Medical Education at Sun Valley. Wed-Sat. Contact: PCMS CME, 705 S 9th, No. 203, Tacoma, WA 98405. (206) 627-7137.

May 13-15—**Idaho Academy of Family Physicians—43rd Annual Meeting.** The Coeur d'Alene, Coeur D'Alene. Mon-Wed. Contact: Mrs Irma Sparks, Exec Dir, IAFP, PO Box 175, Boise 83701.

July 25-27—**Idaho Medical Association—Annual Meeting.** Sun Valley. Thurs-Sat. Contact: IMA, 305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

January 19—**Personality Disorders.** University of New Mexico School of Nursing and Pharmacy Auditorium, Albuquerque. Sat. Contact: Marsha VerPloegh, Psychiatric Medical Association, PO Box 26666, Albuquerque 87125. (505) 291-5375.

February 4-8—**Controversies in Medicine.** Alta, Utah. Mon-Fri. Contact: Neil Kaminsky, MD, New Mexico Mid-Winter Study Group, 717 Encino Place, NE, Ste 9, Albuquerque 87102.

February 15-16—**Southwest Psychiatric Symposium on Substance Abuse.** Hilton Hotel, Albuquerque. Fri-Sat. Contact: University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

March 16—**AIDS Update.** University of New Mexico School of Nursing and Pharmacy Auditorium, Albuquerque. Sat. Contact: Marsha VerPloegh, Psychiatric Medical Association, PO Box 26666, Albuquerque 87125. (505) 291-5375.

May 9-10—**New Mexico Medical Society Annual Meeting.** Albuquerque. Thurs-Fri. Contact: Glenn Taylor, NMMS, 7770 Jefferson NE, Ste 400, Albuquerque 87109. (505) 828-0237 or 1 (800) 748-1596.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

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MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

January 1-6—**Arthritic Hip, Knee & Shoulder** (Sponsor: UUMC). Mon-Fri. Snowbird. Contact: (801) 581-8664.

January 15-19—**Arthroscopic Surgery 1991** (Sponsor: UUMC). Tues-Sat. Phoenix, Arizona. Contact: (801) 581-7602.

January 17-21—**Ethics and Health** (Sponsor: UUMC). Thurs-Mon. University of Utah, Olpin Union Building, Salt Lake City. Contact: (801) 581-8664.

January 25-27—**Laser Surgery—Laparoscopic Cholecystectomy** (Sponsor: UUMC). Fri-Sun. The Laser Institute, University of Utah, Salt Lake City. Contact: J. Freedman, (801) 581-7001.

February 1-3—**Pediatric Update** (Sponsor: UUMC). Fri-Sun. Jackson, Wyoming. Contact: (801) 581-7001.

SPONSORS OF COURSES—ABBREVIATIONS

AHA: American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.

BYUHS: Brigham Young University Health Services, McDonald Student Health Center, Brigham Young University, Provo 84602. (801) 378-2771.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 S 300 East, Salt Lake City 84101. (801) 262-3461.

DMC: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 673-9681.

HCH: Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

144: 144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave, Salt Lake City 84103. (801) 363-1221.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

SMH: St Mark's Hospital, 1200 E 3900 South, Salt Lake City 84117. (801) 268-7111.

UMA: Utah Medical Association, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUMC: University of Utah Medical Center, 50 N Medical Dr, Salt Lake City 84132. (801) 581-2258.

UVRMC: Utah Valley Regional Medical Center, 1034 N Fifth West, Provo 84604. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

VVMC: Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.

February 4-8—**Surgical Pathology** (Sponsor: UUMC). Mon-Fri. Park City. Contact: K. Rassmussen, (801) 379-7178.

February 10-15—**Interventional Radiology** (Sponsor: UUMC). Sun-Fri. Park City. Contact: Judy Gallegos, (801) 581-8188.

February 10-15—**Update in Clinical Microbiology and Immunology** (Sponsor: UUMC). Sun-Fri. Park City. Contact: Midge Beckman, (801) 581-7480.

February 11-16—**Microsurgery Workshop** (Sponsor: UUMC). Mon-Sat. University Park Hotel, Salt Lake City. Contact: (801) 581-8664.

February 11-16—**Orbital & Craniofacial Surgery** (Sponsor: UUMC). Mon-Sat. Snowbird. Contact: (801) 581-8664.

February 11-17—**Family Practice Refresher Course** (Sponsor: UUMC). Mon-Sun. Salt Lake Hilton, Salt Lake City. Contact: K. Chisholm, (801) 581-7234.

February 15-19—**The 35th Anesthesiology Update** (Sponsor: UUMC). Fri-Tues. Snowbird. Contact: V. Larsen, (801) 581-6393.

February 17-20—**The 32nd Annual Ob/Gyn Update** (Sponsor: UUMC). Sun-Wed. The Yarrow, Park City. Contact: S. Martin, (801) 581-5501.

February 19-22—**1991 Winter Ski Meeting and Ophthalmology Update** (Sponsor: UOS). Tues-Fri. Olympus Hotel, Salt Lake City. Contact: UOS.

February 19-23—**Pediatric Emergency Medicine** (Sponsor: UUMC). Wed-Sun. The Marriott Hotel, Salt Lake City. Contact: (801) 588-2000.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

January 10-11—**Alzheimers Update.** Seattle. Thurs-Fri. Contact: U/W.

January 10-11—**Laboratory Safety and Health.** Seattle. Thurs-Fri. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

January 17—**Law and Medicine Symposium.** Tacoma. Thurs. Contact: PCMS CME.

January 17—**Cancer Conference.** Everett. Thurs. Contact: Pacific Northwest Medical Education Institute, (206) 258-5322.

January 19-20—**Advanced Cardiac Life Support Provider Course.** Seattle. Sat-Sun. Contact: VMMC.

January 23—**Pesticide Medicine.** Seattle. Wed. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

January 25-27—**Chest Conference: Lung Day XIX—1991 Annual Meeting.** Leavenworth. Tues-Thurs. Contact: American Thoracic Society, 1 (800) 732-9339.

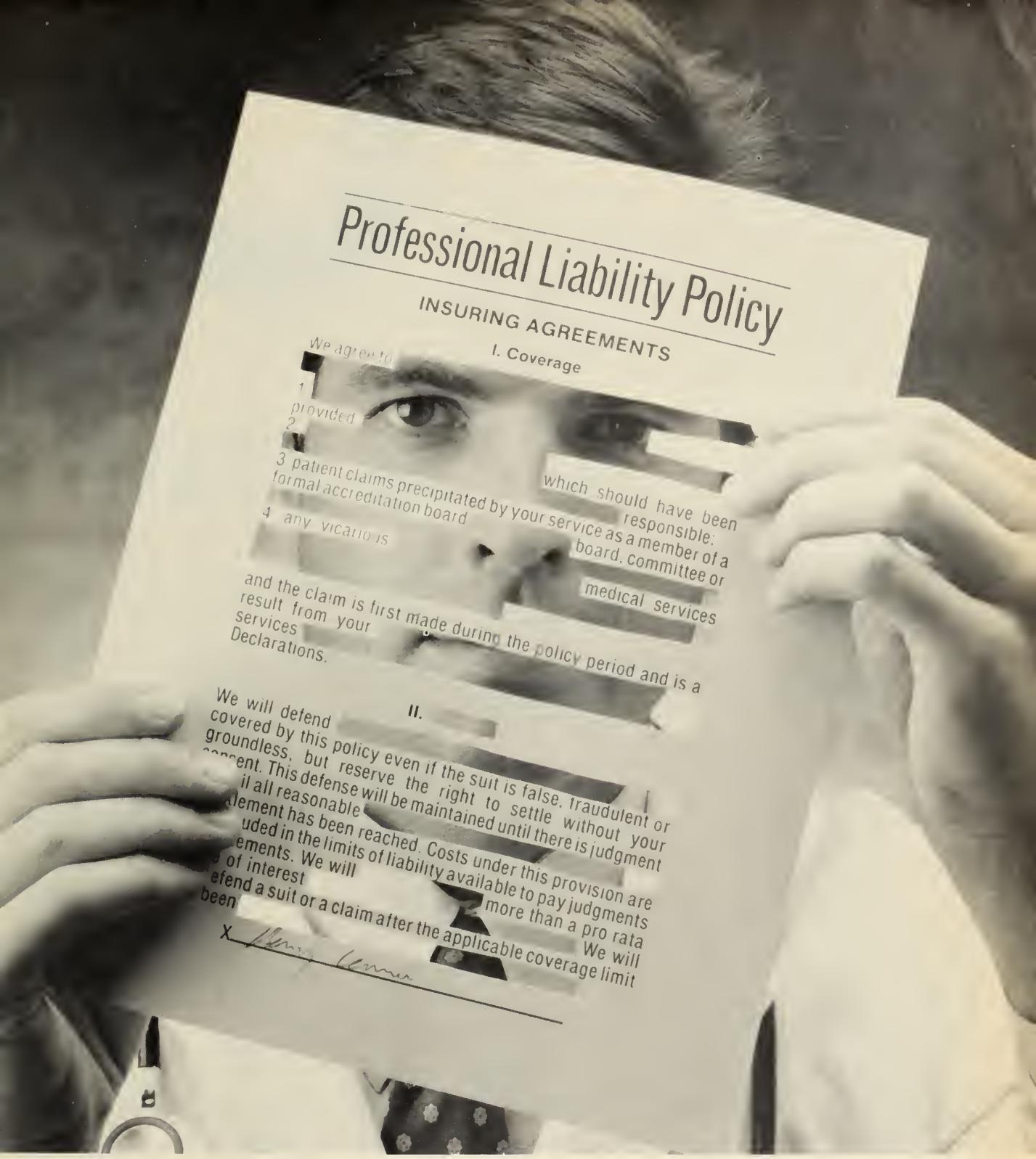
February 8—**Review of HIV Infections.** Tacoma. Fri. Contact: PCMS, (206) 627-7137.

February 22-23—**Arthritis Update.** Seattle. Fri-Sat. Contact: U/W.

February 22-23—**Musculoskeletal Diseases for the Primary Care Physician.** Seattle. Fri-Sat. Contact: U/W.

February 28-March 1—**A Day in the Office: Common Problems in Pediatric Practice.** Seattle. Thurs-Fri. Contact: Group Health, (206) 326-3441.

(Continued on Page 686)



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CONTINUING MEDICAL EDUCATION

(Continued from Page 684)

March 1—**Recent Developments in Occupational Medicine.** Seattle. Fri. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

March 1-2—**Psychiatric and Psychological Issues in Medical Practice.** Seattle. Fri-Sat. Contact: VMMC.

March 13-15—**Spirometry Training for Worker Screening.** Seattle. Wed-Fri. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

March 14-15—**Tacoma Academy of Internal Medicine.** Tacoma. Thurs-Fri. Contact: PCMS CME.

March 14-16—**Emergencies in Older Patients.** Seattle. Thurs-Sat. Contact: U/W.

March 15—**Inflammatory Bowel Disease.** Seattle. Fri. Contact: VMMC.

March 22-23—**Ophthalmology (WSAO)—Annual President's Meeting.** Seattle. Fri-Sat. Contact: (206) 441-9762.

April 2-5—**General Practice Review.** Scottsdale, Arizona. Tues-Fri. Contact: Pacific Northwest Educational Institute, (206) 258-6322.

April 3-4—**Cumulative Trauma Disorders of Upper Extremities.** Seattle. Sun-Mon. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

April 12-13—**Surgical Club.** Tacoma. Fri-Sat. Contact: PCMS CME.

April 12-13—**Low-Back Pain.** Seattle. Fri-Sat. Contact: VMMC.

April 13-14—**Benton-Franklin County Medical Society Annual Meeting.** Tri-Cities. Sat-Sun. Contact: (509) 783-8616.

April 15-18—**The Best Approach 1991: Effective, Efficient Strategies in Cardiology, Orthopedics, Gastroenterology, and Pediatrics.** Kauai Sheraton, Hawaii. Fri-Mon. Contact: Group Health, (206) 326-3441.

April 15-26—**PM & R Review.** Seattle. Fri-Tues. Contact: U/W.

April 26-27—**Medical Issues of Active and Athletic Women.** Seattle. Fri-Sat. Contact: VMMC.

June 1—**Substance Abuse.** Seattle. Sat. Contact: U/W.

June 21—**Horizons in Urology.** Seattle. Fri. Contact: U/W.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

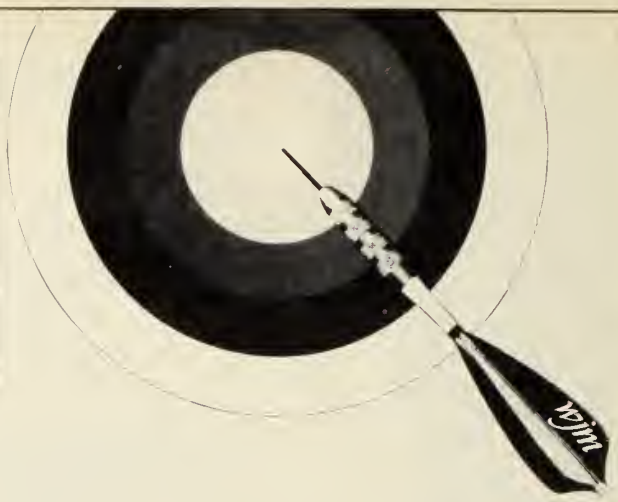
WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

WYOMING

February 1-3—**Pediatric Update.** University of Utah School of Medicine at Jackson. Fri-Sun. Contact: UUMC, 50 N Medical Dr, Salt Lake City, UT 84132. (801) 581—2258.

June 13-15—**Wyoming Medical Society—Annual Meeting.** Jackson Lake Lodge, Moran. Thurs-Sat. Contact: WMS, PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. ◆



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CENTRAL CALIFORNIA. Hospital based teaching opportunity for OB/GYN in a new residency program at the KMC. Ideal candidate is a team player with a strong desire to teach residents. This UCLA affiliate has a busy OB department with 5,000 deliveries per year. Please contact Mary Letterii, Vice President, Physician Search Group, 120 Montgomery St, Ste 710, San Francisco, CA 94104; (415) 399-8840.

INTERNIST—SAN FRANCISCO BAY AREA. An Internist practicing in an East Bay community of 75,000 for the past 37 years is now seeking another Internist to take over his practice. This practice numbers between 400-500, many of whom have been patients for 20 plus years. Send your CV to Gordon Crawford, Professional Relations, Humana Inc, Dept HH-12A, 500 W. Main St, Louisville, KY 40201-1438. Or call toll-free 1 (800) 626-1590.

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(Continued on Page 690)

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(Continued from Page 688)

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You will maintain an active clinical practice with a proportion of time dedicated to leadership and management of physician and support staff. Qualifications must include Board Certification in a clinical specialty and prior management experience.

OBSTETRICIAN/ GYNECOLOGISTS

Part-time, flexible schedules as well as full-time positions are available in Los Angeles and Orange counties.

PRIMARY AND SPECIALTY CARE

A variety of opportunities are available at our 30 health care centers throughout southern California.

We offer a highly competitive compensation and benefits package, malpractice insurance, and continuing medical education. To hear more about CIGNA Healthplan:

Call **(800) 468-9013** or send CV to:
Professional Recruitment Dept.
CIGNA Healthplans of CA
505 N. Brand Blvd, Ste 400-49
Glendale, CA 91203
Equal Opportunity Employer

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CALIFORNIA

Primary Care Physicians and Radiologists needed to work as *locum tenens* statewide. High salary, paid malpractice. Work whenever and wherever you wish. Permanent placements as well. **Western Physicians Registry: Northern California, contact Jim Ellis, Director, (415) 601-7676 or (800) 437-7676. Southern California, contact Tracy Zweig, Director, (805) 643-9346 or (800) 635-3175.**

PREVENTIVE MEDICINE RESIDENCY POSITIONS. The University of California, San Diego-San Diego State University Preventive Medicine Residency Program seeks applicants interested in developing skills in service, teaching and/or research in health promotion and disease prevention for low income and other special populations. The program includes the MPH degree and leads to BE in General Preventive Medicine. African-Americans, Hispanics, and Native Americans strongly encouraged to apply. Letter of interest and CV to Kevin Patrick, MD, MS, Director, UCSD-SDSU General Preventive Medicine Program, San Diego State University, San Diego, CA 92182-0567; or call (619) 594-5332.

DENVER. Primary Care Physician for geriatrics/adults and one BC/BE Internist. $74,294 plus benefits, faculty appointment. Contact: R. J. Brooks, MD, Associate Director, FLMHC, 3520 W. Oxford Ave, Denver, CO 80236; (303) 762-4117. AA/EOE.

WASHINGTON, PUGET SOUND. Part- or full-time Emergency Department practice with low volume, excellent medical staff, and great freedom of scheduling. Malpractice paid. Independent contractor. Send CV to TECP, 955 Tacoma Ave S., Ste 210, Tacoma, WA 98402.

WASHINGTON, PUGET SOUND. Full- or part-time position with expanding physician owned group. Well established, practicing adult Emergency Medicine. High level of Critical Care with excellent medical staff. Great flexibility in scheduling to enjoy the northwest. Partnership potential. Malpractice paid. ABEM certification or preparation required. Send CV to TECP, 955 Tacoma Ave S., Ste 210, Tacoma, WA 98402; (206) 627-2303.

CALIFORNIA, BERKELEY. Experienced Emergency Room, Family Practice, Internal Medicine, and Urgent Care Physicians sought to staff an inpatient service at a large community hospital. Excellent hours (no nights) and compensation. Applicants must be BC/BE in either Emergency Medicine, Family Practice, or Internal Medicine. Job parameters may be configured to accommodate full- or half-time commitments. Please send CV to Joan Wendell, Office Manager, PO Box 5138, Berkeley, CA 94705.

FULL-TIME nontenured track position as an Assistant Professor to work as an attending physician in the Division of Emergency Medicine, Department of Surgery at the University of Utah School of Medicine/Teaching Hospital. Must be residency trained or BC in Emergency Medicine. Reply to MS Linscott Jr, MD, 50 N. Medical Dr, Salt Lake City, UT 84132; (801) 581-2730. Position will be open until January 1, 1991 or until suitable candidate is identified. The University of Utah is an Equal Opportunity Employer.

SOUTHERN CALIFORNIA. Excellent opportunity for aggressive, personable, BC/BE Family Practitioner to join with young, established DO in thriving, recreational, southern California community. Excellent career and income opportunity, generous benefits and incentives. Call (714) 674-6971.

BEAUTIFUL MONTEREY BAY. Immediate opportunity for a friendly, skilled, Family Practice or Emergency Physician to join highly respected Urgent Care group with two beautiful Santa Cruz clinics. Committed to high quality care. Nice people, flexible scheduling, comprehensive benefits, including paid malpractice, group health insurance, long-term disability insurance, no nights, rapid advancement to full partnership in an outstanding place to live. Please send CV to Stuart Simon, MD, 6800 Soquel Dr, Aptos, CA 95003; or call (408) 662-3611.

Longview is a picturesque, stable community of 42,000 located near the Columbia Gorge and the coastal mountains and beaches of Washington and Oregon. Members of our 12 physician group enjoy individual subpractices, infrequent call, and new state-of-the-art medical offices.

We invite you to contact us at the above address regarding practice opportunities. Or call Judy Parmenter, Physician Recruitment, (503) 280-2050 for further information.

ACADEMIC CLINICAL ONCOLOGIST. The Department of Medicine and the Hematology/Oncology Division of the University of California Medical Center, San Francisco is seeking an experienced Oncologist for a full-time academic position at the level of Assistant Clinical Professor. The applicant is expected to have conducted independent clinical research in solid tumor Oncology. Major responsibilities will include teaching in a large fellowship training program and conducting clinical research in the Cancer Research Institute. Candidates should have demonstrated a strong commitment to and excellence in teaching. Correspondence should be directed to Marc A. Shuman, MD, University of California Medical Center, Cancer Research Institute, Box 0128, San Francisco, CA 94143-0128. UCSF is an Equal Opportunity/Affirmative Action Employer. Women and minorities are encouraged to apply.

RADIOLOGIST NEEDED to join one other in a 60-bed hospital based practice with GE 1.5 MRI, 9800 CT, Doppler US, SPECT nuclear, angiography. Excellent salary leading to early partnership. Unique opportunity to join a sophisticated practice while living among the redwoods in a northern California coastal city with a referral population of over 100,000. Send CV to Dr Jackson, 3560 N St, Eureka, CA 95501; (707) 445-5993.

INTERNAL MEDICINE PRACTICE. Seek American trained, BC Internist to time share, for time control and quality medicine. Excellent hospital facilities and medical staff. Outstanding living area. Contact S. Johnson, MD, 721 Sheridan Ave, Cody, WY 82414; (307) 527-6415.

BC/BE INTERNIST needed to share practice/call with three others in busy and attractive community. Cody, Wyoming is located only 50 miles from Yellowstone National Park. Area abundant in fishing, hunting, and outdoor sports. No state income tax! 181-bed multi-service facility which includes Acute, Long Term Care, and Chemical Dependency Center. For more information call Ruth McDaniel, CEO at (307) 578-2488 or send CV to West Park Hospital, 707 Sheridan Ave, Cody, WY 82414. EOE.

FAMILY PRACTICE—Washington, California, Nevada, Texas, Louisiana, Florida! Private practice opportunities available with established physicians or groups. For details, call Eloise Gusman, 1 (800) 535-7698 or send CV to PO Box 1685, Covington, LA 70434-1685.

INTERNAL MEDICINE—Nevada, Texas, Louisiana, Florida. Private practices available with established physicians or groups. For details, call Eloise Gusman, 1 (800) 535-7698 or send CV to PO Box 1685, Covington, LA 70434-1685.

MEMORIAL CLINIC offers excellent opportunity for BC/BE Family Practitioner to establish a second Family Practice neighborhood clinic. OB optional. Competitive salary and excellent benefits. Send CV to Memorial Clinic, Attention Inge Hart, 500 Lilly Rd, N.E., Olympia, WA 98506; (206) 456-1122, ext 249.

OB/GYN, INTERNISTS, Family Practitioners, Pediatricians for Arizona and western opportunities. Quality positions available other regions of country. Inquiries confidential. Mitchell & Associates, PO Box 1804, Scottsdale, AZ 85252; (602) 990-8080.

NORTHERN CALIFORNIA—SAN FRANCISCO BAY AREA. Leading HMO is seeking BC/BE physician to staff a busy, urban, full-service Emergency Department with the possibility of administrative advancement. Kaiser Permanente is a large pre-paid HMO offering competitive salary, job security, shareholder status and generous benefits including health care, life insurance, disability insurance, sick leave, mortgage assistance, and educational leave. Please address all inquiries to David Witt, MD, Emergency Department, Kaiser Permanente Medical Center, 1200 El Camino Real, AD-WJM, South San Francisco, CA 94080-3299; or call (415) 742-2516. EOE.

OCCUPATIONAL MEDICINE PHYSICIAN. Modesto Occupational Medical Clinic is looking for a full-time physician. We are a young, thriving high-volume practice in need of an additional physician who is BC/BE or with experience in Occupational Medicine. We are a full service clinic with x-ray, Physical Therapy, and all equipment for Occupational Monitoring. We have a large client company base with several years of experience. This person must have good clinical skills, be highly motivated, be energetic, and looking for a challenging career. Position may include administrative and clinic responsibilities with opportunity for partnership. We are located in the central valley two hours from both San Francisco and several excellent ski resorts in the Sierra Nevada. Please contact Susan Hooper, 1600 Sunrise, Ste 16, Modesto, CA 95350; (209) 529-6234.

ORTHOPEDIC SURGEON. University of California, San Francisco seeks a BC/BE Orthopedic Surgeon to fill a faculty/staff position at the Valley Medical Center, Fresno. The Orthopedic Department at VMC supports a busy Trauma Service and actively participates in teaching residents in General Surgery, Emergency Medicine, and Family Practice. This position also offers private practice opportunities in a setting within the faculty group. Competitive salary and benefits. The central California location offers affordable and enjoyable year-round recreational living. Address inquiries and CVs to H. B. Morgan, Jr, MD, Chief of Orthopedics, 2212 N. Winery, #130, Fresno, CA 93703. EO/AA employer, women and minorities are encouraged to apply.

INTERNIST—SAN FRANCISCO. Full-time or part-time position available for Internist or Family Practitioner to practice in an innovative, nationally recognized HMO for frail elderly. Malpractice paid. Competitive salary and excellent benefits. Reply with CV to Catherine Eng, MD, On Lok Senior Health Services, 1441 Powell, San Francisco, CA 94133; (415) 989-2578. EOE.

EUROPE. Limited number of Primary Care Physicians for care of American families. One year term. Renewal option, no weekends, substantial benefits, tax advantages. Leave message. (408) 773-9250. All calls returned.

FAMILY PRACTICE, BC/BE to join group practice in growing southwestern town. Full service clinic, 280-bed hospital. Offering competitive salary, equal call schedule, partnership. Contact Myrna Hughes, Arizona Western Medical Center, 2149 W. 24th St, Yuma, AZ 85364; (602) 344-1400.

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PHYSICIANS NEEDED

The continuing growth of our service area population (now 90,000) has created an immediate need for additional BC/BE physicians in the following specialities:

- **NEUROLOGY.** Establish private practice with no investment, guaranteed income. Proficiency in EEG, EMG required.
- **GENERAL/THORACIC SURGERY.** Establish private practice in General and Thoracic Surgery (no open heart) with no investment, guaranteed income.
- **ONCOLOGY.** Establish private practice with no investment, guaranteed income. Some General Internal Medicine necessary initially.
- **ORTHOPEDIC SURGERY.** No investment, guaranteed income. Above average earning potential.
- **RADIOLOGY.** Hospital group position. Excellent salary and benefit package. Competency in ultrasound, CAT, Nuclear Medicine, film screen mammography, and general diagnosis required. MRI experience desired. Inpatient and outpatient. (California license is required.)
- **PEDIATRICIAN.** Join busy private Pediatric Practice. Attractive salary with arrangements for future association.
- **FAMILY PHYSICIAN.** Join busy four Family Practice group in private practice. Salary or guarantee first year.

112-bed full service hospital, very well equipped. Excellent ancillary services. Our service area population is now 90,000; a growing area with new businesses and a stable economy.

Located in central California near Sequoia National Park, Tulare offers an excellent family oriented lifestyle and all expected amenities. Beautiful homes, close to hospital and office, are affordably priced. Good schools, many community activities, and abundant recreation including golf, tennis, skiing, mountain and equestrian activities. Easy access to all California's major metropolitan and resort areas.

Contact:

Tulare District Hospital
Physician Recruiting Office
PO Box 90112
Los Angeles, CA 90009
(800) 468-2687

RADIOLOGIST. Part-time position available immediately in small hospital with general Radiography and Fluoroscopy, Mammography, and Ultrasound in Weaverville, California. Contact Drs Wheeler, Biggs, or Babbitt, West Coast Radiology, 3798 Janes Rd, Ste 12, Arcata, CA 95521; office number (707) 822-3621, ext 191.

SOUTHERN CALIFORNIA. 300-bed hospital in growth community at foothills of Mt Baldy. Opportunity for OB/GYN, Family Practice, and Rheumatologist to associate with successful practitioners. Hospital will provide generous guarantee, moving expenses, and practice management assistance. Please contact Ken Baker, Physician Search Group, 120 Montgomery St, Ste 710, San Francisco, CA 94104; (415) 399-8840.

PEDIATRICIAN, BC/BE to join group Family Practice/Pediatrics. Growing community with growing pediatric population. Active Nursery Level II hospital and nursery with NNP coverage. Offering competitive salary, equal call schedules, partnership. Contact Myrna Hughes, Arizona Western Medical Center, 2149 W. 24th St, Yuma, AZ 85364; (602) 344-1400.

CARDIOLOGIST. BE/BC to join busy two person Cardiology group on the Los Angeles west side. Excellent opportunity for the active practice of clinical, consultative, invasive, and noninvasive Cardiology plus UCLA teaching affiliation. David Ciraulo, MD, 323 N. Prairie, Inglewood, CA 90301.

ReadiCare, Inc

ReadiCare currently has numerous opportunities in California and Washington state for qualified physicians. We offer:

- Flexible hours and days
- No on-call or mandatory weekends
- Competitive salary plus bonus plan
- Paid vacation, sick holiday and CME
- 401(k) Plan
- Full medical/dental
- Relocation assistance

Contact:

Marilyn Burke
(800) 237-3234
ReadiCare, Inc
PO Box 2457
Santa Clara, CA 95055

GREATER SEATTLE. BC/BE General Internist needed to join busy, office-based Primary Care Practice 30 minutes north of Seattle. Quality of life superb with weekend call one in six and unlimited recreational opportunities within minutes. Financial potential excellent. Prefer full-time but will consider part-time to start. Reply to Number 229, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602 with CV and cover letter. Interview expenses will be paid.

CALIFORNIA—NAPA. Attention General Practitioners, Family Practitioners, Internists, Emergency Room Physicians: Napa State Hospital has two full-time positions for medical/surgical on-duty coverage, 4:30 pm to 8:30 am (16 hour shift, ten days per month). No responsibility for psychiatric call. Salary $77,472 to $85,224 annually, with raise on January 1, 1991. Benefit package approximately 33% additionally. Napa State Hospital has a large (100 plus) well trained medical staff, intensive on-campus CME, and a university affiliated research unit. EOE, Affirmative Action, physicians union. Send CV to Jeffrey Zwerin, DO, Medical Director, Napa State Hospital, 2100 Napa-Vallejo Hwy, Napa, CA 94558-6293; telephone (707) 253-5434. In California; 1 (800) 421-0666.

FAMILY PRACTICE-HOSPITAL SPONSORED CLINIC OPPORTUNITY. Dynamic, growth oriented hospital in beautiful north central Wisconsin is seeking Family Physicians to respond to growing community demand. The administrative burdens of medical practice will be minimized in this hospital managed clinic. The hospital has committed to an income and benefit package which is significantly higher than similar opportunities. Package includes base income, incentive bonus, malpractice, disability, signing bonus and student loan reduction/forgiveness program. All relocation costs will be borne by the hospital. Please contact Kari Wangsness, Associate, The Chancellor Group, Inc, France Place, Ste 920, 3601 Minnesota Dr, Bloomington, MN 55435; (612) 835-5123.

SAN FRANCISCO BAY AREA BC/BE INTERNISTS

We are currently seeking highly qualified Internists and subspecialists to complement our energetic Internal Medicine team. Department members provide a full range of medical services for a population of over 200,000 pre-paid health plan members. Recently renovated and expanded medical center facilities are within convenient commuting distance to virtually any bay area city, and the extensive cultural and recreational activities of northern California. As part of our large, multispecialty group practice, you would enjoy an excellent salary, generous fringe benefits, a flexible schedule, and the opportunity for academic affiliation with prestigious local institutions. Send CV to:

Winslow Wong, MD
Attn: Administration
Kaiser Permanente Medical Center
27400 Hesperian Blvd
Hayward, CA 94545

EOE

SEATTLE: BC/BE General Internist to join BC Internists' group with three Seattle area offices. No income guarantee; group and location excellent. Call or write Douglas Bovee, MD, 3203 W. McGraw, Seattle, WA 98199; (206) 285-3139.

FAMILY PRACTICE RESIDENCY DIRECTOR and full-time faculty position for BC Family Physician in an 18 resident, eight faculty program affiliated with University of California, Davis. Large clinical component with inpatient, outpatient, and routine OB skills needed. Send inquiries to T. N. Ernst, MD, PO Box 231, Merced, CA 95340-0231; (209) 385-7172.

EMMETT, IDAHO, rural community of 5,000 (12,000 in county) located 25 miles from Boise, is seeking residency trained Family Practitioner to enter full-time practice. First year salary guarantee $60,000 with incentive. Located close to several downhill ski areas as well as many other recreation opportunities such as hunting, fishing, camping. Inquires: please call Newton States, Hospital Administrator; (collect) (208) 365-3561.

SACRAMENTO—BE/BC General Internists. Successful stable multispecialty group. Opportunity to practice full range of inpatient and outpatient Internal Medicine. Full access to diagnostic, therapeutic, and consultative services. Academic affiliation with University of California, Davis, teaching residents in our hospital. In house CME. We are Kaiser Permanente—a physician managed, well established steadily growing group. Outstanding starting salary and advancement, benefit package, and retirement. Sacramento is California's boom town. Excellent schools. Family life-style. This is a quality career opportunity. Please call or send CV to Dennis Ostrem, MD, The Permanente Medical Group, Inc, 2025 Morse Ave, Sacramento, CA 95825; (916) 973-5781. EOE.

SACRAMENTO AREA. Immediate opening for BC/BE Family Practice Physician to join busy seven member group. Guaranteed salary and excellent benefit package. Partnership offered after two years. Opportunity to practice full range of primary medicine including Pediatrics, Geriatrics, and inpatient care. Excellent community to practice medicine with affordable housing, excellent schools, and state of the art hospital facilities. Send CV to Craig Lyon, 1219 30th St, Sacramento, CA 95816; (916) 737-0226.

WASHINGTON. Openings for career oriented Emergency Physicians, BC in Emergency or Primary medical specialty. Seattle metropolitan hospital with 54,000 annual visits. Excellent salary in a stable growing group. Contact Dan Hiatt in care of Linda Johnson, 8009 S. 180th, Ste 110, Kent, WA 98032; (206) 575-2595.

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PHYSICIANS WANTED

WASHINGTON STATE

ROCKWOOD CLINIC, PS

An expanding 70 physician multispecialty fee-for-service group seeks BC/BE physicians in the following specialties:

ALLERGY
CARDIOLOGY
DERMATOLOGY
INTERNAL MEDICINE
PEDIATRICS
URGENT CARE CENTER—
FAMILY PRACTICE
OCCUPATIONAL MEDICINE
HEMATOLOGY/ONCOLOGY
NEPHROLOGY
RHEUMATOLOGY
ORTHOPEDICS

seeks Emergency Medicine and Family Practice Physicians (BC/BE).

Attractive benefit package includes competitive salary leading to early shareholder status.

CONTACT: **Colleen Mooney, Recruitment Coordinator**
Rockwood Clinic, PS
E. 400 Fifth Ave
Spokane, WA 99202
(509) 838-2531

COME ENJOY SPOKANE'S QUALITY LIFE-STYLE!

INTERNIST—PACIFIC NORTHWEST. Excellent opportunity for BC/BE Internist to join group of five Internists in suburban Idaho community. Near urban referral center with good subspecialty backup. Also near superb hunting, fishing, camping, and skiing. Please call or refer résumé to Susan Davis, Administrator, Caldwell Internal Medicine Professional Association, 222 E. Elm, Caldwell, ID 83605; 1 (208) 459-4667.

INTERNIST—SIERRA FOOTHILLS. Excellent opportunity to establish busy practice in growing retirement community. Join dynamic, three BC Internist call group in Grass Valley-Nevada City, with unsurpassed medical facilities, recreational and cultural opportunities. Contact Brad Miller, MD, 970 E. Main St, Grass Valley, CA 95945.

FAMILY PRACTICE PHYSICIAN—CALIFORNIA. Two full-time positions available for physicians in a group practice setting located in central California. Salary very competitive, excellent benefits package and paid malpractice. Additional benefits negotiable including relocation expenses, school loan retirement, possible loan(s) repayment based on longevity. This rural/suburban community location offers easy access to mountain and coastal communities as well as major cities. Please call collect at (415) 226-1421 and ask for Steven R. Grant, Placement Director, or send CV to MRA—Medical Recruitment Group, 43157 Gallegos Ave, Ste A, Fremont, CA 94539.

CHEYENNE, WYOMING. Immediate opening available for a dedicated, career oriented, full-time Emergency Physician with Urgent Care facility in Cheyenne, Wyoming. Competitive compensation plus malpractice insurance. Approximately 14 days per month, standard 12 hour shifts. Excellent living conditions, high quality school system, moderate taxes and living expenses, exciting recreational opportunities in the heart of the Rocky Mountain region. Call now for additional information or send CV to Janet Cowley, Recruitment Coordinator, PO Box 805, Cheyenne, WY 82003; (307) 632-1436, FAX (307) 635-4642.

OPPORTUNITY FOR GENERAL SURGEON with Thoracic and Vascular experience. Salary leading to partnership. Northern California surgical group in northern California rural community. Excellent quality of life. 1165 S. Dora, A3, Ukiah, CA 95482; (707) 462-7579.

UNIVERSITY OF CALIFORNIA, DAVIS MEDICAL CENTER. The University of California, Davis, Department of Emergency Medicine is searching for physicians residency trained or BC in Emergency Medicine. The Health Science Campus is located in Sacramento and serves a large area of northern California. The Emergency Department cares for over 60,000 patients a year. The Center operates as a Level One Trauma Center, has paramedic base station training responsibilities, and has a helicopter service. An approved Emergency Medicine Residency Program began in July 1990. Emergency Physicians supervise medical students, interns, and residents, in addition to having direct patient responsibilities. Support for clinical research is available to those interested. University compensation is competitive, and fringe benefits include health and dental insurance, three weeks paid vacation, one week continuing medical education, social security, UC retirement plan, 12 paid holidays per year, and full malpractice coverage. Send CV to Robert W. Derlet, MD, Chief, Division of Emergency Medicine, University of California, Davis, Medical Center, 2315 Stockton Blvd, Sacramento, CA 95817.

RADIOLOGIST—SAN FRANCISCO BAY AREA. Growing outpatient imaging practice with CT/MRI. Salary leading to partnership. Send CV to Murray Solomon, MD, 450 Sutter St, Ste 835, San Francisco, CA 94108; (415) 296-8654.

PEDIATRICIAN BC/BE for hospital-based teaching practice. Interest and training in Neonatology and Critical Care Pediatrics preferred. Join three full-time Pediatricians, two full-time Neonatologists, and one full-time Pediatric Surgeon in hospital with Community Level NICN and busy inpatient and outpatient services. Paid malpractice. Salary negotiable based on training and experience. Submit CV and references to Patricia A. Dixon, MD, Director, Pediatrics/Neonatal Services, San Joaquin General Hospital, PO Box 1020, Stockton, CA 95201; (209) 468-6600. AA/EOE.

BC/BE INTERNIST NEEDED. Opportunity to join part of a comprehensive medical group practice located in the suburbs of San Francisco. Professional setting of 36 physicians. Forward CV to Peter Earley, Physician Relations, Ross Valley Medical Group, 2200 Larkspur Landing Circle, Ste 103, Larkspur, CA 94939.

PHYSICIANS WANTED

Western States OPENINGS
Many multispecialty groups and hospitals have asked us to recruit for over 300 positions of various specialties. Both permanent and locum tenens. Send CV to:
Western States Physician Services
5414 E. Montecito, Fresno, CA 93727
Or call 1 (800) 873-0786

SAN FRANCISCO. Primary Care Practice in Noe Valley seeks BC/BE Family Practitioner or Internist to join growing practice. Competitive salary, wonderful neighborhood, partnership option. Send résumé to Noe Valley Family Medicine, 3700 24th St, San Francisco, CA 94114.

FAMILY PRACTICE RESIDENCY FACULTY POSITION—CASPER, WYOMING. University of Wyoming Family Practice Residency-Casper is seeking an experienced, clinically oriented, BC Pediatrician to be the Pediatric Coordinator of an 8-8-8 Family Practice residency program. Level II Nursery skills are a must. 60% teaching, 20% direct patient care, 20% research. This is a tenure track position. University approval will be required prior to filling this position. Come join us in beautiful Wyoming. The University of Wyoming is an affirmative action/EOE. Contact Dr David Driggers, Director, University of Wyoming Family Practice Residency, 1522 E. "A" St, Casper, WY 82601; (307) 266-3076.

SACRAMENTO, URGENT CARE. $120,000 guaranteed at free standing, hospital affiliated clinic with an annual census of 18,000. Prestigious northern California group seeks qualified, experienced physicians, BC or BP in specialty. Additional opportunities at two area hospitals' ED Fast Tracks. Paid malpractice and generous profit sharing. Contact Art Wong, MD, FACEP, Emergency Physicians' Medical Group, 120 Montgomery, Ste 1000, San Francisco, CA 94104; (415) 989-1242.

SAN FRANCISCO BAY AREA—Occupational Health/Ambulatory Care center, Monday through Friday days; no nights, weekends or holidays required. Seeking Family Practice or Emergency Medicine experienced physician with keen interest in Occupational Medicine. Salary $100K plus. Send CV to Chase Dennis Group, 400 Taylor Blvd, #330, Pleasant Hill, CA 94523; (415) 676-2555.

ATTENTION ADVERTISERS!

The deadline for submitting classifieds for the February issue of WJM is December 18.

Send your advertisement to:

Classified Advertising
WJM, PO Box 7602
San Francisco, CA 94120-7602

(415) 882-3376

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FAMILY PRACTITIONER OTOLARYNGOLOGIST PEDIATRICIAN

Multispecialty group located in San Luis Obispo, California, seeks BC/BE physicians. Fringe benefits plus practice costs paid and shareholder status. Submit your CV to:

Physician Recruitment
San Luis Medical Clinic
1235 Osos St
San Luis Obispo, CA 93401

FAMILY PRACTICE—SACRAMENTO. Kaiser Permanente is seeking BC/BE Family Practice Physicians to join the Division of Family Practice. We offer a challenging position that provides both outpatient and inpatient experience and enjoys close support from the specialty departments. We offer our patients high quality medicine and our physicians a practice with a high degree of professional and personal satisfactions. You will be joining a unique organization with a long, successful track-record and will benefit from the financial security associated with its success. Sacramento is a large diverse city providing a relative low cost of housing and is rich in cultural activities. It is also 90 miles from San Francisco and Lake Tahoe recreation areas. For additional information contact Stuart Hahn, MD, The Permanente Medical Group, Inc, 3240 Arden Way, Sacramento, CA 95825; or call (916) 973-5546. EOE.

STAFF PHYSICIAN. Join us in providing comprehensive medical care for 330 developmentally disabled children and adults at the Wyoming State Training school. Three physicians and one physician's assistant staff our 18-bed health care center and provide medical support to nursing, therapists, professional and paraprofessional staff across campus. Good working relationships with excellent hospital and medical group in local community. Progressive habilitation-oriented working environment. Attractive benefits, malpractice insurance provided, no overhead. Annual salary range $50,000 to $70,000 depending upon experience and qualifications. Campus situated in pleasant west-central Wyoming community of Lander, minutes from beautiful Wind River Mountain Range and close to Yellowstone and Grand Teton National Parks. Outstanding hiking, fishing, hunting, skiing, wilderness areas nearby. Good schools and services, low cost of living, no state income tax. Contact Director of Clinical Services, Wyoming State Training School, 8204 State Highway 789, Lander, WY 82520; or call (307) 332-5302. Equal Opportunity Employer.

COASTAL CALIFORNIA 45,000 population. Well-trained 12 physician Primary Care group. Immediate/future need for Family Practice and Internal Medicine. Competitive salary and benefits with partnership after one year. On call schedule allows time for family and recreation. In Lompoc, you can do what you were trained to do, including OB, Pediatrics, and General Medicine. Please contact Ken Baker, President, Physician Search Group, 120 Montgomery St, Ste 710, San Francisco, CA 94104; (415) 399-8840.

OREGON. General Internal Medicine and Family Practice, BC/BE, sought for 10 member, multispecialty group in beautiful rural community, population 16,500, 38 miles southwest of Portland. Send CV to Administrator, 420 E. Fifth St, McMinnville, OR 97128; (503) 472-6161.

ORTHOPEDIC SURGEON. Immediate opening available for associate Orthopedic Surgeon. Established Orthopedic Practice in North Hollywood, close to St. Joseph Medical Center. For information call office manager Lizzy Regester (818) 506-0999.

CALIFORNIA

Primary Care Physicians and Radiologists needed to work as *locum tenens* statewide. High salary, paid malpractice. Work whenever and wherever you wish. Permanent placements as well. **Western Physicians Registry: Northern California, contact Jim Ellis, Director, (415) 601-7676 or (800) 437-7676. Southern California, contact Tracy Zweig, Director, (805) 643-9346 or (800) 635-3175.**

CENTRAL CALIFORNIA MULTISPECIALTY. Internist, Cardiologist, Dermatologist, Pediatrician, Orthopaedic Surgeon. 43 physician multispecialty group in beautiful city of 75,000, 45 minutes from Sierras, three hours from Los Angeles and San Francisco. Fee-for-service practice. Salary guarantee plus incentive, all corporate fringes. BC/BE only. Contact Gerald Moore, Administrator, Visalia Medical Clinic, Inc, 5400 W. Hillsdale Dr, Visalia, CA 93291; (209) 733-5222.

ARIZONA. Thomas-Davis Medical Centers, PC, a rapidly expanding multispecialty group practice of 110 plus physicians in Tucson, Green Valley, and Phoenix, Arizona has positions available in these cities in Family Practice, Internal Medicine, and Pediatrics. Excellent fringe benefits and profit sharing program. Guarantee for first two years, plus incentive. Early shareholder. Fee-for-service, as well as physician owned HMO. Must be BC/BE. Call or write Bill De Long (602) 322-2525 or James J. Vitali, CEO, (602) 322-2525 at Thomas-Davis Medical Centers, PC, PO Box 12650, Tucson, AZ 85732.

PEDIATRICIAN BC/BE needed in northern suburb of San Francisco. Opportunity to join part of a multispecialty group. Applicant should demonstrate strong academic skills committed to quality personalized care. Forward CV to Peter Earley, Physician Relations, Ross Valley Medical Group, 2200 Larkspur Landing Circle, Ste 103, Larkspur, CA 94939.

GREAT OPPORTUNITIES IN NORTHERN CALIFORNIA. We are San Jose's leading multispecialty private group practice, and want a BC/BE physician with broadly based high level training to join our Department of Urgent Care and General Medicine. The position offers competitive salary plus incentive bonus, a comprehensive benefits package including retirement and 401K plan contributions, and early access to partnership and stockholder status. The south bay area provides a wide range of cultural and recreational activities, good schools, fine dining, and a congenial climate. We're growing, and we'd like to hear from you. Send your CV to Maureen Forrester, San Jose Medical Group, 45 S. 17th St, San Jose, CA 95112; or call us at (408) 282-7833.

IMMEDIATE OPENINGS

General Surgeon

◆◆◆

Family Practice

◆◆◆

Internal Medicine

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(Continued on Page 695)

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Director of Ambulatory Care
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P.O. Box 8113
San Luis Obispo, CA 93403-8113

(805) 549-4936

INTERNIST: Administration/patient care/teaching/opportunity for research. Position as Chief, Medical Service, at VA Medical Center, Reno, Nevada and assistant to full professor, Department of Medicine, University of Nevada School of Medicine. This jointly funded position requires a BC Internist, eligible for licensure in Nevada, with management interest and experience. Teaching responsibilities involve medical students and residents. Send CV and letter of interest to Dr Miles Standish, Associate Dean, University of Nevada School of Medicine, Reno, NV 89557-0046. The University of Nevada and the Department of Veterans Affairs are equal opportunity employers.

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Area brochure available upon request.

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SKI—CME EUROPE or HELI-B.C. $25.00. Rainier Educational Emprize. T. Akamatsu, MD, 502 N. Stadium Way, Tacoma, WA 98403; (206) 572-4619.

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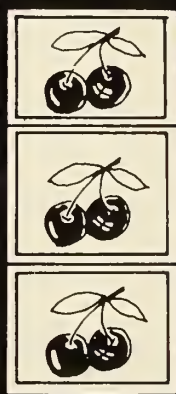

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$80.00 including lunch

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The Arthritis Foundation
4311 Wilshire Blvd., Suite 530
Los Angeles, CA 90010

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CONFERENCES

THE MONTEREY HEALTH COMMUNICATION CONFERENCE, "Continuing the Conversation: Communication and Health." March 5-10, 1991, at the Double Tree Inn, Fisherman's Wharf, Monterey, California. Fees: Prior to February 15, 1991: General—$200; Including CME's and other CEU's—$275; Health Network Members and Students (written proof of full-time student status)—$150. A $50 late fee will be charged for all registrations received after Feburary 15, 1991. For information contact The Health Communication Research Institute, 1050 Fulton Ave, Ste 105, Sacramento, CA 95825; or call (916) 483-1583.

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January 31-February 2, 1991

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Lois Gibson, St. Charles Medical Center
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CONFERENCES

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For complete registration information, contact:

Specialty/G.P. '91: A Meeting of the Minds
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Phone: (604) 669-7175
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Arizona Medical Association, Inc—810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: June 6-8, 1991, Loews Ventana Canyon Resort, Tucson.

California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 8-13, 1991, Bally's Grand Hotel, Reno.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 20-22, 1991, Snowmass.

Hawaii Medical Association—1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: 1991, date and location to be announced.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: 1991, date and location to be announced.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: 1991, date and location to be announced.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 25-28, 1991, Quail Lodge, Carmel, California.

New Mexico Medical Society—7770 Jefferson, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: May 9-10, 1991, The Marshall Building, Albuquerque.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting (House of Delegates only): April 26-28, 1991, Salisham.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: 1991, date and location to be announced.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: 1991, date and location to be announced.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 13-15, 1991, Jackson Lake Lodge, Moran.

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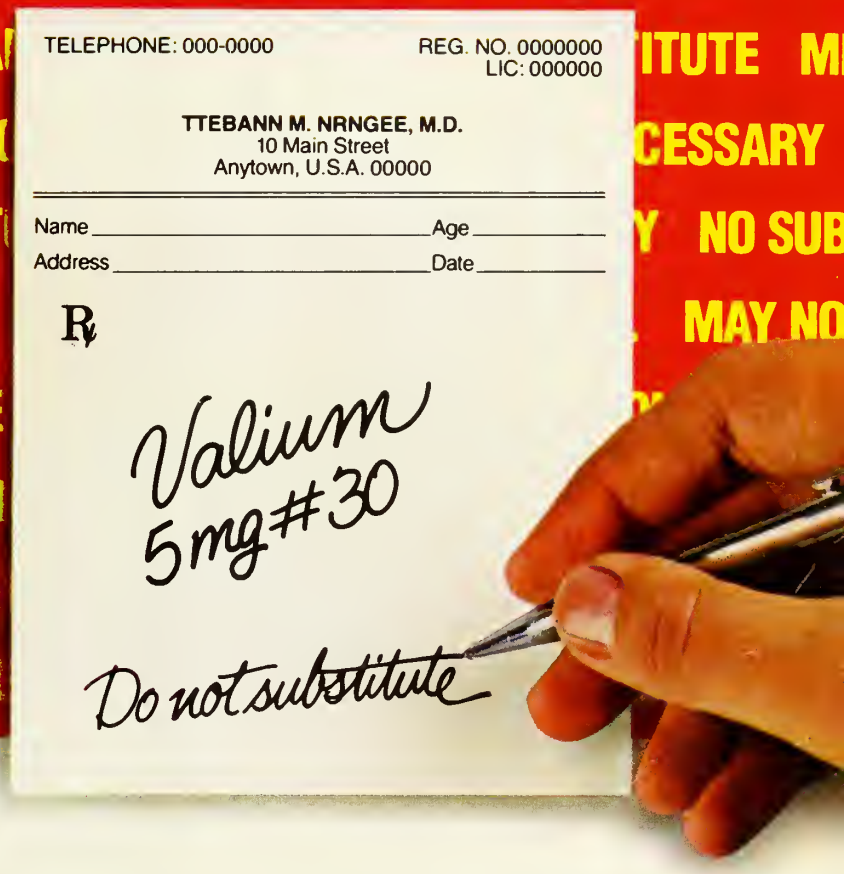

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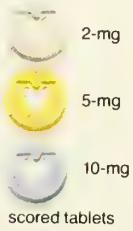

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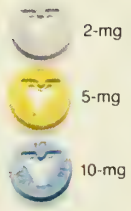

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